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INNOVATION FOR DISEASES THAT MAINLY AFFECT DEVELOPING COUNTRIES: ISSUES AND IDEAS

This note provides a brief summary of recent thoughts and discussions on stimulating the development of new medicines, vaccines and diagnostics for diseases that are particularly prevalent in developing countries.

INNOVATION EXAMINED

Medical innovation—the development of new diagnostics, vaccines and treatments—is an important factor in addressing the burden of disease, and there is widespread agreement that it should continue. Moreover, scientific progress, exemplified by the decoding of the human genome, appears to hold enormous promise for the development of new and better medicines. Yet this promise has thus far failed to materialize; the number of new drugs entering the market appears to be decreasing rather than increasing. There also are concerns that the number of products in research and development (R&D) pipelines is insufficient.[1]

Detailed reviews have furthermore drawn attention to the fact that of 1 393 new drugs approved between 1975 and 1999, only 16 (1%) were specifically developed for tropical diseases and TB—diseases that account for over 10% of the global disease burden.[2]

Dissatisfaction with this state of affairs led the World Health Assembly in 2003 to set up an independent Commission on Intellectual Property Rights, Innovation and Public Health (CIPIH). Its main mandate was to "produce an analysis of intellectual property rights, innovation and public health, including the question of appropriate funding and incentive mechanisms for the creation of new medicines and other products against diseases that disproportionately affect developing countries".[3] Members of the CIPIH were drawn from academia, the public health community and the pharmaceutical industry. The CIPIH published its report in April 2006.

[1] United States Food and Drug Administration. Challenge and opportunity on the critical path to new medical products. Rockville, 2004.

[2] Patrice Trouiller et al. Drug development for neglected diseases: a deficient market and a public health policy failure. *Lancet 2002*; 359: 2188-94.

[3] World Health Assembly Resolution WHA 56.27, May 2003.

Box 1. Terms of Reference of the CIPIH

- Summarize the existing evidence on the prevalence of diseases of public health importance with an emphasis on those that particularly affect poor people and their social and economic impact;
- Review the volume and distribution of existing research, development and innovation efforts directed at these diseases;
- Consider the importance and effectiveness of intellectual property regimes and other incentive and funding mechanisms in stimulating research and the creation of new medicines and other products against these diseases;
- Analyse proposals for improvements to the current incentive and funding regimes, including intellectual property rights, designed to stimulate the creation of new medicines and other products, and facilitate access to them;
- Produce concrete proposals for action by national and international stakeholders.

IPR, INNOVATION AND INCENTIVES

The main mechanism to stimulate the development of new medicines is via intellectual property rights (IPR), especially patents—and this has been so for several decades. A patent provides a time-limited monopoly. During the monopoly period, the company that developed the drug (and holds the patent) can sell it at a relatively high price, since there is no competition. Thus, it is during this time that the innovator company that developed the drug earns the most profit from it. These profits, in turn, motivate the innovator to continue investing in research and development (R&D).

The amount of profit depends on the profit margin and the sales volume. However, if only a few people need a particular drug, or if the people who need the drug cannot afford to buy it, sales will be low. As a result, the company will not earn much–maybe not even enough to recover the costs of developing the drug.

Intellectual property rights therefore do not—and cannot be expected to—provide effective incentives for the development of new medicines for diseases that mainly or exclusively affect the poor. Nor do they provide sufficient incentives for the development of medicines for 'orphan' diseases, that is, rare diseases that affect only a small number of people.

But whereas basic medical research (the "R" in R&D) is conducted in public institutions as well as the private sector (pharmaceutical industry), the development of

new products (the "D" in R&D) is almost exclusively undertaken by the pharmaceutical industry. Thus the industry determines to a large extent which new medicines will be developed and marketed, and which ones will not. For companies this is a commercial decision.[4] And because the IPR system's incentives are linked to sales, companies prioritize the development of medicines for which there is a viable market. The development of medicines for "diseases that disproportionately affect developing countries" gets accorded a low priority—and, as mentioned above, very few such medicines have been developed in the last three decades.

This should not come as a surprise. Nor should the pharmaceutical industry be blamed for what is an inherent limitation of the intellectual property system.

Means and Objectives

It is important to bear in mind that intellectual property rights are a policy tool. The objective is to stimulate innovation.

Yet intellectual property rights have failed to achieve their objective with regard to the development of medicines for diseases that mainly affect developing countries, such as HIV/AIDS, malaria, TB, leishmaniasis and trypanosomiasis. Policy-makers therefore ought to consider making adjustments, or complementing intellectual property rights with other measures.

A prerequisite for inducing positive change is to identify alternative mechanisms. This is one of the issues—and probably the one closest to its mandate—that the CIPIH looked at. The main alternatives considered by the CIPIH are listed below.

Possible alternative mechanisms to fund R&D

Growing awareness of the limitations of IPR to provide incentives to stimulate R&D for diseases that mainly affect the poor, has led to several proposals to address this problem. Some of those ideas have been developed further than others, and some are more radical than others. The main ideas are summarized below.[5]

- *Public-private partnerships*: These partnerships bring together donors, researchers and private sector actors. The private sector usually contributes 'in kind' expertise and is involved in screening for drug candidates. Most partnerships focus on a specific issue or disease; examples include the Medicines for Malaria Venture and the Global Alliance for TB Drug Development. Others, such as the Drugs for Neglected Diseases Initiative, target several diseases.

  Public-private partnerships have successfully revitalized R&D in some disease areas that were previously neglected. It is however too early to assess whether these partnerships will succeed in effectively developing new products and making them affordable enough to improve the options for prevention and treatment in developing countries. Moreover, the long-term sustainability of such partnerships is often not ensured.

- *"Sensible" patenting and licensing strategies*: Public research and funding institutions should bear in mind the importance of access to products created based on their inventions, and should adjust their strategies for patenting and licensing accordingly. For example, they could decide not to apply for patents in developing countries. Or they could insist on non-exclusive licensing of their inventions/the inventions they fund, thereby enabling competition and facilitating access. Since public institutions often focus on 'upstream' inventions, this would furthermore facilitate the downstream development of health care products.

  Spurred by students, initiatives along these lines—albeit with a focus on access rather than innovation—have garnered support from prominent academics and are being considered by some university technology managers. At least one major pharmaceutical company has announced that, as a matter of policy, it will not file new patent applications in least-developed countries, nor will it enforce its existing patents in those countries.

  A leading university in the United States of America has proposed that a broad research exemption be included in licences granted over its patented inventions; this would allow all universities and public research institutions to use those inventions for research purposes. Several other universities have licensed technologies relevant for the development of treatments for Chagas disease, malaria and TB on favorable terms to non-profit enterprises or public-private partnerships.

  Moreover, in France, Germany and the United States, rules have been introduced to prevent the granting of overly broad patents on genetic inventions,[6] which could hinder further research and innovation. In the United States of America, the National Institutes of Health have developed draft guidelines that, as a general rule, support non-exclusive licensing of genetic inventions.[7]

- *Patent pools*: A patent pool is an arrangement between several patent holders for the collective management of their patents. Patent pools can be voluntary or imposed by governments. By pooling patents for (certain areas of) medical research, licensing

[4] It should however be noted that companies do at times develop or take part in the development of medicines for 'diseases of poverty', among others for philanthropic reasons.

[5] For more details, see pages 66-68, 88-94 and 104-107 of the CIPIH report.

[6] Note however that views differ as to whether genetic 'inventions' are inventions or discoveries; in the latter case they are not patentable.

[7] United States National Institutes of Health. Best practices for the licensing of genomic inventions. Washington, 2004.

procedures can be centralized and streamlined[8]. The CIPIH recommends this strategy especially for research tools. It is anticipated that, when implemented, patent pools would make access to research tools easier, which in turn would facilitate research in both the public and private sector.

The idea of a patent pool is in fact not new; in 1917, the Government of the United States created a mandatory pool of patents that were crucial for the continued development of the aircraft industry. More recently, patent pools have been used in the area of DVD-video and DVD-ROM technology. A patent pool has also been proposed to facilitate access to biotechnology patents.[9]

Box 2. Practicalities pertaining to patent pools

A patent pool can be defined as "the aggregation of intellectual property rights which are the subject of cross-licensing, whether they are transferred directly by the patentee (patent holder) to licensee or through some medium, such as a joint venture, set up specifically to administer the patent pool."[10]

Patent pools can eliminate problems caused by 'blocking' patents, make it easier and faster to obtain licences and reduce transaction costs (e.g. by reducing or eliminating the need for litigation). This, in turn, can accelerate the development of new technologies and products.

Patent pools have been criticized for their potential anti-competitive effect—but it has equally been recognized that they can facilitate competition. In the United States, guidelines exist that specify when a patent pool would be anti-competitive, and when it is pro-competitive.[9]

- *Advance purchase commitments*: The idea is to create a market where there is none, by guaranteeing in advance the purchase of a drug or vaccine that does not yet exist (e.g. a malaria vaccine). It is believed that if the amount and price are high enough, and the commitment originates from credible organizations with sufficient financial backing, this would provide an incentive for the development of the desired medicine. Procedural issues are yet to be clarified.

  The International AIDS Vaccine Alliance (IAVI) and the Global Alliance for Vaccines and Immunization (GAVI) are considering whether an advance market commitment could play a role in the development of respectively an AIDS vaccine and a vaccine for pneumonia strains commonly encountered in developing countries. Meanwhile, several of the G8 countries have recently pledged funds for a pilot project with advance market commitments.[11]

- *Prize fund*: A "prize fund" is in fact a variation on the idea of an advance purchasing commitment. Instead of rewarding innovators indirectly, via profits on the sale of the final product, a prize fund would directly pay a significant sum as a reward or "prize" to whoever invented a new drug or vaccine for specified diseases. Thus, the innovator would directly be rewarded for his or her invention. The prize would have to be substantial in order to be effective. Here, too, procedures need to be clarified.

  But procedural issues can be addressed; in the United States, a Bill to this end has been drafted.[12] Meanwhile, experiments have started as well: one large pharmaceutical company has set up an independent virtual research and development laboratory. This reportedly successful laboratory operates online and offers prizes for solutions to specific problems in biology and chemistry.[13]

Box 3. A "prize fund" experiment?

On Innocentive's website (http://www.innocentive.com/), "seeker" companies and scientists interact in a marketplace. Companies post specific problems (see examples below), and offer rewards for a solution. Reportedly, over US$ 1.5 million has been paid out over a four year period, and more than 90 000 scientists have registered with the site.[14]

INNOCENTIVE 3084371 Detection of specific DNA sequences POSTED: Nov 04, 2005 DEADLINE: Under Evaluation US$ 5 000 Ideas for rapid and simple detection of specific DNA sequences are needed.	INNOCENTIVE 3159934 Identification of an enzyme POSTED: Dec 06, 2005 DEADLINE: Mar 07, 2006 US$ 50 000 Identification of an enzyme with specific properties is required.	INNOCENTIVE 3060616 DNA separation POSTED: Oct 19, 2005 DEADLINE: Feb 20, 2006 US$ 40 000 A method to separate DNA molecules is needed.

[8] A patent pool would act as a 'one-stop-shop' to obtain a license for all patents relevant to the research that will be undertaken.

[9] Jeanne Clark et al., "Patent pools: a solution to the problem of access in biotechnology patents?", United States Patent and Trademark Office, White Paper, December 2000.

[10] Joel I Klein, United States Department of Justice, quoted in Clark et al (footnote 9).

[11] G8. Fight against infectious diseases. G8 Summit, St Petersburg, 16 July 2006.

[12] H.R. 417, The Medical Innovation Prize Fund Act, was introduced to the United States House of Representatives by Representative Sanders on 26 January 2005.

[13] William C Taylor, "Here's an idea: let everyone have ideas", *New York Times*, 26 March 2006.

[14] *New Scientist*, 8 April 2006, p. 59.

- *Medical R&D treaty*: The basic idea of an R&D treaty is that governments commit to spending a certain percentage of the national income on medical R&D, but would be free to decide the mechanism for doing so. Governments would be able to choose the current IPR system, or to fund medical research directly, or to select any of the mechanisms listed above. If a government for example would opt to directly fund research (e.g. by giving grants to research institutions or via a prize fund), it would not have to respect patents on pharmaceuticals, since the country would already have paid its fair share of medical R&D.

Most of these proposals and ideas need to be developed and examined further, with a critical but open mind—and efforts to do this are already taking place. Moreover, it should be borne in mind that this is not an exhaustive list; it merely is a brief overview of some of the main ideas that have been assessed by the CIPIH.

THOUGHTS ON THE WAY FORWARD

The fact that all but one of the above-mentioned suggestions are already being considered or tried out seems to indicate that they may have potential. The exception is the "R&D treaty", which is not being tried or tested, since the majority of countries are—via international (trade) treaties and/or other obligations—locked into the current IPR system.

At the same time, some of the proposals have been criticized for lack of evidence that they will work. This is true, but new and innovative approaches suffer by definition from such a lack of evidence. There is however evidence that the current IPR system is not particularly successful in delivering new treatments for diseases that disproportionately affect developing countries.

Box 4. Dubious proposals

Several ideas have been examined and discarded by the CIPIH. These include:

- *orphan drug schemes*: developed originally in the United States, these schemes have successfully provided incentives for the development of medicines for rare diseases. One of their main features is the provision of exclusive marketing rights, which provide an incentive since the target population, while small, has the ability to pay. But it is unlikely that such schemes would effectively stimulate the development of medicines for which there is no market;
- *tax credits/tax reduction*: such schemes cannot be expected to work where there is no market and hence no profit to be made (and no tax to be paid);
- *transferable IPR*: if a company develops a drug for a 'disease of poverty' (on which it will not make a profit), it would be rewarded by an extension of the patent term of another, existing drug of its choice on which it is making a profit. However, this essentially means solving one problem by creating another.

It must be underlined that these proposals are not mutually exclusive; rather, they should be seen as a menu of options. The challenge is to find the right mix, at the national and global level.

Moreover, none of the ideas listed above seek to replace or abandon the IPR system. Rather, they are attempts to fine-tune its implementation or to create alternatives that can be implemented side-by-side. Contrary to the belief of some, even the R&D treaty does not seek to abandon the IPR system per se; any country would be free to choose IPR as its preferred mechanism to fund R&D. The treaty would simply provide countries with other ways and means—that may be better suited to their domestic capacity and priorities—to achieve the objective of encouraging medical R&D.

Box 5. Expanding the clinical trial infrastructure

Other CIPIH recommendations focus on expanding the infrastructure and capacity to conduct clinical trials in developing countries. If implemented, this could accelerate late stage development and marketing of products already in the pipeline. It could also facilitate product development by national companies in developing countries—though as long as they are subject to the prevailing commercial incentives there is little a priori reason to believe that these companies will specially target 'diseases of poverty'. Meanwhile, expanding the infrastructure and capacity for clinical trials will, by itself, probably do little to increase (basic) innovation in developing countries.

FURTHER READING

1. CIPIH. *Public Health, Innovation and Intellectual Property Rights*. Geneva: WHO, 2006. Available at http://www.who.int/intellectualproperty/en/
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3. Patrice Trouiller, et.al. Drug development for neglected diseases: a deficient market and a public health policy failure. *Lancet* 2002; 359: 2188-94.
4. Roy Widdus. Product development partnerships on 'neglected diseases': How they handle intellectual property and how this may contribute to improving access to pharmaceuticals for HIV/AIDS, TB and Malaria. ICTSD paper, 2004. Available at http://www.iprsonline.org/unctadictsd/bellagio/dialogue2004/bell3_documents.htm
5. International AIDS Vaccine Initiative. Advance Market Commitments: helping to accelerate AIDS vaccine development. Policy brief no. 9, November 2005. Available at http://www.iavi.org/viewpage.cfm?aid=1377
6. Burton A Weisbrod. Solving the drug dilemma. *Washington Post*, 22 August 2003.
7. Joseph Stiglitz. Give prizes not patents. *New Scientist*, 16 September 2006.
8. Tim Hubbard, James Love. A New Trade Framework for Global Healthcare R&D. *PLoS Biology* 2004; 2(2):147-150. Available at http://biology.plosjournals.org

ADDENDUM

CIPIH recommendations pertaining to alternative mechanisms to fund R&D

The report of the Commission on Intellectual Property Rights, Innovation and Public Health (CIPIH) contains a number of specific recommendations pertaining to alternative mechanisms for encouraging medical R&D for diseases that disproportionately affect developing countries. These recommendations are listed below.

"Sensible" patenting and licensing strategies (Recommendation 2.7)

Countries should seek through patenting and licensing policies to maximize the availability of innovations, including research tools and platform technologies, for the development of products of relevance to public health, particularly to conditions prevalent in developing countries. Public funding bodies should introduce policies for sensible patenting and licensing practices for technologies arising from their funding to promote downstream innovation in health-care products.

Patent pools (Recommendation 2.8)

Patent pools of upstream technologies may be useful in some circumstances to promote innovation relevant to developing countries. WHO and WIPO should consider playing a bigger role in promoting such arrangements, particularly to address diseases that disproportionately affect developing countries.

Public-private partnerships (Recommendations 3.2 and 3.3)

To enhance the sustainability of public–private partnerships:

- Current donors should sustain and increase their funding for R&D to tackle the health problems of developing countries.
- More donors, particularly governments, should contribute to increase funding and to help protect public–private partnerships and other R&D sponsors from changes in policy by any major donor.
- Funders should commit funds over longer time frames.
- Public–private partnerships need to continue to demonstrate that they are using their money wisely, that they have transparent and efficient mechanisms for accountability, that they coordinate and collaborate, and that they continue regularly to monitor and evaluate their activities.
- The pharmaceutical industry should continue to cooperate with public–private partnerships and increase contributions to their activities.
- Research institutions in developing countries should be increasingly involved in executing research and trials.

WHO should initiate a process to devise mechanisms that ensure the sustainability and effectiveness of public–private partnerships by attracting new donors, both from governments and the private sector, and also to promote wider participation of research institutions from developing countries. However, governments cannot passively rely on what these partnerships could eventually deliver; there is a need for a stronger commitment on their part for an articulated and sustainable effort to address the research gaps identified in this report.

Advance purchase commitments (Recommendation 3.5)

Governments should continue to develop forms of advance purchase schemes which may contribute to moving later stage vaccines, medicines and diagnostics as quickly as possible through development to delivery.

Medical R&D treaty (Recommendation 3.6)

Recognizing the need for an international mechanism to increase global coordination and funding of medical R&D, the sponsors of the medical R&D treaty proposal should undertake further work to develop these ideas so that governments and policy-makers may make an informed decision.