'An R&D framework would address the question of who pays for essential medical R&D, dissociating incentives from drug prices and rewarding innovation according to health-care outcomes'

editorial

Nathan Ford*

Ellen 't Hoen

Tido von Schoen-Angerer

Discussions in Geneva, demonstrations in Delhi: why incentives for drug innovation need reviewing

In May 2007, health ministers from all member states of the World Health Organisation will meet at the World Health Assembly in Geneva to discuss the crisis in the current drug development system. Across the developing world, patients and governments struggle to access new essential medicines that are too expensive. At the same time, health care workers in tropical countries struggle to treat common health problems with old, outdated medicines because too few new ones are being developed [1].

The central question is the impact of intellectual property in promoting innovation and access to medicines. Most governments today provide strong intellectual property protection laws for pharmaceuticals, but this was not always the case. Up until recently, many governments considered medicines to be too important to be subject to market monopolies. As recently as the early 1990s, 48 countries (including Finland, Spain and Portugal) chose to exclude pharmaceutical products from patentability. Since 1996, however, the World Trade Agreements have globalized patent protection for pharmaceuticals by establishing minimum universal standards in all areas of intellectual property. Governments that previously provided no or limited patent protection for pharmaceuticals must now, as World Trade Organization (WTO) members, provide patent protection for a minimum period of 20 years [2].

Providing intellectual property protection for pharmaceuticals means implementing a system that minimizes or excludes competition and results in higher drug prices. Although governments who wanted to be part of the WTO had to accept this, it was argued that they would benefit in several ways, notably through increased technology transfer, increased foreign investment in the pharmaceutical sector and increased drug development. These benefits are now being questioned. A ten-year study from Thailand found no increase in technology transfer and foreign investment as a result of increased patent protection [3]. As we discuss here, neither has the rate of innovation improved, particularly in the area of developing world diseases.

Lack of access, lack of innovation

Lack of access and lack of innovation are two sides of the same coin. The patent system is being increasingly criticized on both counts.

1359-6446/06/$ - see front matter doi:10.1016/j.drudis.2007.03.008

Access to medicines is limited by the fact that, since the implementation of the WTO Agreements, all new medicines are subject to patent protection, and this is driving up the price of treatment in many disease areas; there is little or no competition for newer medicines and companies offer only limited discounts to a limited number of countries [4]. Flexibilities exist within the current WTO rules that allow governments to override pharmaceutical patents whenever they limit access, but their use is strongly opposed. For example, in February 2007, the Thai Government, concerned about the high cost of patented versions of antibiotics, and drugs for HIV, cancer, cardiovascular and neuropathic problems, issued compulsory licenses to access generic versions of these medicines. This move is consistent with WTO and national law, but drug companies, backed by some Western country governments, were quick to try and block these efforts [5]. One company, Abbott, has gone so far as to refuse to register any new medicines in Thailand until the Thai Government reverses its position on intellectual property [6].

At the same time, the promise of more innovation that came with the globalization of patent rules has failed to deliver new products for neglected diseases. Between 1975 and 2004, of the 1,556 new chemical entities marketed globally, only 20 new drugs (1.3%) were for tropical diseases and TB, which account for 12% of the global disease burden [7]. One example of the consequences of this neglect is TB, which kills up to 2 million people annually. The current treatment strategy, based on drugs that date from the 1960s, is long and demanding (daily treatment for at least six months) and compromised by increasing drug resistance [8]. Similarly, treatment for two common tropical diseases, African sleeping sickness and visceral leishmaniasis (each responsible for 60,000 deaths a year), relies on drugs that are archaic, toxic and increasingly ineffective owing to drug resistance [9]. There has been some progress in recent years, notably through the work of public-private partnerships for neglected-disease drug development, but such initiatives are too few and too poorly funded [10].

The poor performance of the patent system in stimulating innovation is not just a problem for the developing world. A survey that assessed >3,000 new products approved for the French market between 1981 and 2004 concluded that 68% of them brought 'nothing new' compared to previously available preparations [11]. In Canada, a similar study rated barely 5% of all newly patented drugs as 'breakthrough'. Drugs classified as offering no added therapeutic benefit over existing drugs were responsible for 80% of the rise in prescription costs in Canada [12]. According to the United Nations Development Programme, <5% of drugs introduced by the top 25 pharmaceutical companies in the USA represented true therapeutic advances; of these, 70% were developed with Government involvement [13].

Another issue is the exploitation of weaknesses in national patent systems by companies to gain intellectual property protection for products that do not merit it. Today, many drug patents are being disputed across the globe. A patent application for valgancyclovir, a drug used to treat cytomegalovirus infection in transplant and HIV patients, is currently in dispute in Brazil. In Thailand, strong opposition by patient groups has led to a patent application for the combination drug zidovudine–lamivudine to be withdrawn [14], while another AIDS drug patent, for didanosine, was overturned [15]. In keeping with trade rules, India amended its Patents Act in 2005 to allow patents for pharmaceutical products to be granted only for real innovations. Novartis is now challenging the Indian patents act in the Indian court, and Indian patient groups have launched a campaign to defend the law. As of March 2007, more than a quarter of a million people from around the world had signed a petition calling for Novartis to drop its legal action against the Indian Government [16].

Towards a global framework for needs-driven drug R&D

It is this crisis in the patent system that led >280 scientists from 50 countries, including five Nobel Prize winners, to write to the WHO in January 2006 to push for the development of an alternative framework for drug R&D. The authors noted: 'At a time of huge progress in basic research science, and more money being spent on biomedical R&D than ever, we are deeply concerned about the ability of existing mechanisms to translate this into a global improvement in public health [...] We see research activities increasingly complicated by legal restrictions, such as intellectual property rights, which can interfere with free data exchange and can limit biomedical research progress. We do not see a good balance between medical need and resource allocation in the existing system to support R&D'[*].

Later that year, the WHO Commission on Intellectual Property, Innovation, and Public Health (CIPIH) released its report [17]. The report, a result of over three years of research, confirmed the trend that, whereas patent protection has increased over the past ten years through the implementation of the WTO agreements, and further reinforced through bilateral and regional trade agreements, innovation has declined in quantity and quality. Moreover, no evidence was found that the provision of pharmaceutical patents in developing countries is boosting innovation for diseases mainly affecting people in these countries.

The Commission concluded that access and innovation had to be addressed together, and put forward alternatives to patent rewards, such as prize funds [18], with the aim of stimulating R&D without relying on drug sales to fund drug development. The Commission also recommended that the WHO monitors the public health impact of intellectual property on drug development and access, and suggested developing a plan of action to secure funding for developing drugs for diseases of the less-developed world. It also made the point that governments must have a more proactive role to ensure that health R&D meets real needs, rather than commercial interests.

These recommendations now need to be translated into actions through political commitment. Following on from the recommendations of the Commission, the WHO established an Intergovernmental Working Group to examine ways to stimulate innovation while improving access [19]. Within these discussions, several developing countries are calling for a global R&D framework treaty that would ensure that all participating governments contribute to R&D for medical innovation in a way that would guarantee availability and affordability. Further discussions will take place at the World Health Assembly in May, and throughout 2007. However, one year since the establishment of the Intergovern-

[*] Anon. (2006) Letter submitted 25th January 2006 to members of WHO Executive Board, Geneva Switzerland.http://homepage.ntlworld.com/thubbard/whoscientistsletter/English%20Letter.html.

mental Working Group, there has been little progress. It is time to be more concrete.

As these political discussions move forward, pharmaceutical companies will need to decide where they stand. There are signs that some companies are willing to explore new ways to be rewarded for their investments into R&D that do not automatically shut out the world's poor. At a two-day symposium on TB drug development in New York in January 2007[†], representatives from several major pharmaceutical companies, including GSK and Novartis, endorsed a statement supporting the current discussion at the WHO for an alternative R&D framework. Such a framework would address the question of who pays for essential medical R&D, dissociating incentives from drug prices and rewarding innovation according to health care outcomes.

Companies need to engage constructively in this effort to explore new ways to reward investments into R&D that are not biased against the world's poor. With an increasing number of patent disputes breaking out across the globe, and increasing governmental concern that the current system is failing to deliver, it is in everyone's interest that new mechanisms are found, and soon.

References

1 Pécoul, B. *et al.* (1999) Access to essential drugs in poor countries: a lost battle? *JAMA* 281, 361–367
2 World Trade Organization (2001) *Declaration on the Trips Agreement and Public Health*, WTO http://www.wto.org/english/thewto_e/minist_e/min01_e/mindecl_trips_e.htm.
3 Supakankunti, S. *et al.* (2001) Impact of the World Trade Organization TRIPS Agreement on the pharmaceutical industry in Thailand. *WHO Bull* 79, 461–470
4 Ford, N. *et al.* (2007) Treating HIV in the developing world: getting ahead of the drug development curve. *Drug Discov. Today* 12; 1/2
5 Treerutkuarkul, A. (2007) Ministry pushes ahead with patent breaking. *Bangkok Post*, 13 February
6 Zamiska, N. (2007) Abbott escalates Thai patent rift. Firm pulls plans to offer new drugs in spat with regime. *Wall St. J.* 14 March
7 Chirac, P. and Torreele, E. (2006) Global framework on essential health R&D. *Lancet* 367, 1560–1561
8 Moran, M. (2005) *Running Out of Breath – TB Care in the 21st Century*. Médecins Sans Frontières
9 Veeken, H. and Pécoul, B. (2000) Drugs for 'neglected diseases': a bitter pill. *Trop. Med. Int. Health* 5, 309–311
10 Moran, M, *et al.* (2005) *The New Landscape of Neglected Diseases Drug Development*, LES/Wellcome Trust (http://www.wellcome.ac.uk/assets/wtx026592.pdf)
11 Anon, (2001) A look back at 2000: Overabundance and deregulation. *Prescrire Int.* 10, 52–54
12 Morgan, S.G. *et al.* (2005) 'Breakthrough' drugs and growth in expenditure on prescription drugs in Canada. *Br. Med. J.* 331, 815–881
13 Anon. (1999) *Human Development Report*, United Nations Development Programme (http://hdr.undp.org/reports/global/1999/en/)
14 Anon. (2006) HIV drug fears. Hundreds rally at Glaxo office. UK firm's move for patent on Combid is 'a threat to access of cheap medicines. *Nation*, 8 August
15 Ford, N. *et al.* (2004) The role of civil society in protecting public health over commercial interests: lessons from Thailand. *Lancet* 363, 560–563
16 Mueller, J.M. (2007) Taking TRIPS to India – Novartis, patent law, and access to medicines. *N. Engl. J. Med.* 356, 541–543
17 't Hoen, E. (2006) Report of the Commission on Intellectual Property Rights and Health: a call to governments. *WHO Bull.* 84, 1–3
18 Stiglitz J. (2006) Give prizes not patents. *New Sci.* 16 September
19 Anon. (2006) *Public Health, Innovation, Essential Health Research and Intellectual Property Rights: Towards a Global Strategy and Plan of Action*, World Health Organisation (http://www.who.int/gb/ebwha/pdf_files/WHA59/A59_R24–en.pdf)

Nathan Ford*
Médecins Sans Frontières, Town One Properties, Sulani Drive, Khayelitsha 7784, South Africa
nathan.ford@mweb.co.za

Ellen 't Hoen
Tido von Schoen-Angerer
Médecins Sans Frontières, rue de Lausanne 78, 1211 Geneva, Switzerland

[†] Anon. (2007) No time to wait. Overcoming the gaps in TB drug development Conference Statement, New York, 15 January. Available at: http://www.accessmed–msf.org/prod/publications.asp?scntid=1512007115307&contenttype=PARA&.