Saturday 13 September 2003

BMJ

New deal from the World Trade Organisation

May not provide essential medicines for poor countries

On 30 August 2003 the World Trade Organisation (WTO) announced that it had resolved the issue of giving poor countries "access to essential medicines" without breaching its own law on intellectual property. The WTO's 1994 agreement on trade related aspects of intellectual property, TRIPS, makes 20 year patent protection mandatory, allowing drug companies to charge monopoly prices for essential medicines. TRIPS has built-in measures that allow countries to over-ride patent protection for public health purposes but since 2001, WTO members have been trying to reach agreement about what this flexibility means in practice. Argument has centred on the question of "compulsory licensing," which allows countries to over-ride patents and manufacture cheaper generic versions, and the extent to which producers of generic drugs can export to poor countries that have insufficient manufacturing capacity, without the risk of trade courts imposing trade sanctions.

A WTO declaration in 2001 stated the organisation's intention of finding an interpretation that squared the interest of pharmaceutical industries and developing countries.[1] Last week's announcement sets out the terms on which countries such as India and Brazil can export to least developed countries cheaper, generic versions of patented drugs for HIV/AIDS, tuberculosis, malaria, and the occasional infectious disease.

With the fifth WTO ministerial conference taking place on 10-14 September in Cancun, Mexico, the organisation's new director general, Supachai Panitchpakdi, has described the deal as a historical agreement. Members' freedom to decide their own health policy unencumbered by trade policies has been high on the list of controversies that sank the 1999 negotiations in Seattle. But some WTO watchers are sceptical. They point out that the deal reached last week is based on the same declaration that the European Union originally opposed because it did not think access to drugs would be made any easier for poor countries.[2]

There are good grounds for scepticism. TRIPS is not a treaty that benefits less developed countries. Industrial countries hold 97% of all patents worldwide, and 80% of patents granted in developing countries belong to residents of industrial countries.[3] TRIPS was originally pushed through by the US government with threats of trade sanctions against non-compliant countries and is not likely to be given up lightly.[4] Last week's agreement reduces the flexibility within the treaty, limiting a health emergency—one of the grounds for invoking the treaty's flexibilities—to three main diseases, whereas the 2001 declaration of intent said an accommodation should be reached for all public health issues.[5] Limiting policy autonomy in this way reinforces the drive to vertical, drug based programmes and moves away from attempts to build more universal and comprehensive integrated health systems.

There are also more basic problems with TRIPS. Its mandatory norm of 20 years' patent protection means that a company can exploit its monopoly position to charge higher prices over a longer period than it would be able to charge were there competitors. The rationale is that monopoly pricing will allow producers to recoup the costs of investment in research and development and reap a profit, thereby leading to additional new medical innovations and social gains despite the higher costs. Last week's agreement reiterates support for the monopoly pricing principle.[6]

But the UK Commission on Intellectual Property Rights and Development Policy questioned in 2002 whether a global norm for patent protection is in the best interests of developing countries[7] and whether an individual or company should be able to take out a patent on products that have important societal implications.[8] It stated that intellectual property is of little relevance in stimulating research and development of diseases prevalent in developing countries. It points out that less than 5% of the money spent worldwide on pharmaceutical research and development is for diseases that predominantly affect developing countries. Although expenditure on total pharmaceutical research and development in the private sector doubled to $44bn in 1990-2000, of the 1395 drugs approved between 1975 and 1999, only 13 were specifically indicated for tropical diseases, including tuberculosis and malaria.[9] Concluding that the research agenda for pharmaceuticals is led by market demands of the developed world rather than the needs of poor people, the commission recommended that intellectual property rules should limit the scope for patenting that serves more to protect markets, and exclude competition, than promote local research and development.

In recommending more public funding for research the commission also noted the recent encouragement by the developed world of patenting in state funded research institutions and universities. The UK commission recommends that most developing countries, particularly those without research capabilities, should strictly exclude diagnostic, therapeutic, and surgical methods from patentability, including new uses of known products. It says that developing countries

BMJ 2003;327:571–2

should limit the scope of subject matter that can be patented and provide extensive safeguards to ensure that patent rights are not exploited inappropriately. The agreement signed on 30 August 2003 falls far short of this recommendation.

Lastly the UK commission, again, has drawn attention to the complexity of the legal and administrative architecture of the WTO and the way in which developing countries are disadvantaged in the negotiations and by the absence of civic dialogue and public debate.[7] Until these issues are put at the top of the WTO agenda the real effect of this and any future trade rounds will continue to be the entrenchment of the interests of western countries and their industries.

Allyson M Pollock *professor*
(allyson.pollock@ucl.ac.uk)

David Price *senior research fellow*

Public Health Policy Unit, School of Public Policy, University College London, London WC1H 9QU

Competing interest: None declared.

1 WTO. *Declaration on the TRIPS agreement and public health.* Geneva: WTO, 20 November 2001 (WT/MIN(01)/DEC/2).
2 Raghavan C. Medicines won't be cheaper under TRIPS and public health decision. Geneva: Third World Network, 31 Aug 2003. www.twnside.org.sg/title/5409b.htm (accessed 7 Sep 2003).
3 Koivusalo M, Rowson M. Who will inherit the earth? *Health Matters* 2000;41. www.healthmatters.org.uk/stories/rowson2.html (accessed 8 Sep 2003).
4 Braithwaite J, Drahos P. *Global business regulation.* Cambridge: University Press 2000:39-87.
5 WTO takes first step. *Lancet* 2003;362:753.
6 WTO. *Implementation of paragraph 6 of the Doha declaration on TRIPS and public health.* Geneva: WTO, August 2003 (W/TL/540).
7 Commission on Intellectual Property Rights. *Integrating property rights and development policy.* London: CIPR, 2002. www.iprcommission.org/graphic/documents/final_report.htm (accessed 8 Sep 2003.)
8 Drahos P. Biotechnology patents, markets and morality. *European Intellectual Property Review* 1999;21:441-9.
9 Trouiller P, Olliaro P, Torreele E, Orbinski J, Laing R, Ford N. Drug development for neglected diseases: a deficient market and public health policy failure. *Lancet* 2002;359:2188-94.

What are all the things that aspirin does?

This fascinating but simple and cheap drug has an assured future

Ask any medical student and he or she will tell you that aspirin reduces fever, pain, and inflammation but may cause ulcers. Students may also recollect that it prolongs bleeding, and may prevent strokes and heart attacks, but would be unlikely to know of its use in cancer or Alzheimer's disease.

A defining point in the history of aspirin was the discovery that it inhibited the prostaglandin forming cyclo-oxygenase.[1] Prostaglandins cause inflammation, fever, and pain; have gastric cytoprotective actions; and are implicated in platelet aggregation, so this discovery provided a unified explanation for the effects of aspirin (and most other non-steroidal anti-inflammatory drugs). However, events took an even more interesting turn when a further isoform of cyclo-oxygenase, cyclo-oxygenase-2, was discovered.[2] While similar in many ways to the original enzyme (COX 1) there were important differences, including the fact that COX 2 was induced in cells by inflammatory insults. COX 2 therefore seemed to be the most relevant target in inflammation, which led to the notion that the constitutive COX 1 generated prostaglandins required to maintain physiological functions (such as protection of the gastric mucosa, platelet aggregation) whereas COX 2 generated pro-inflammatory mediators.[3] Aspirin inhibited both isoforms, as did most non-steroidal anti-inflammatory drugs, perhaps explaining why these compounds were not only effective therapeutically but also had characteristic side effects.

The ensuing search by the pharmaceutical industry for selective COX 2 inhibitors culminated in the recent introduction of new, safer anti-inflammatory drugs as well as the rediscovery of older drugs that had COX 2 selective actions. But, as aspirin inhibits both isoforms, why does it continue to be used and why is there continuing interest in its pharmacology?

The answer to the first part of this question is partly down to aspirin's unique mechanism of action that inhibits both COX 1 and COX 2 irreversibly. The effects of this are evident in platelets where cyclo-oxygenase cannot be replaced, explaining why a single aspirin can depress platelet aggregation for many days. The half life of aspirin in plasma is short; esterases remove the acetyl group leaving free salicylate, which may have a secondary pharmacological effect through cyclo-oxygenase inhibition or other mechanism, adding to the complexity of aspirin's action.

The current interest in aspirin stems from the fact that many animal experiments and human epidemiological studies now link aspirin (and other non-steroidal anti-inflammatory drugs) with beneficial effects in various cancers, including breast, ovarian, oesophageal, and colorectal cancer. Recent meta-analyses supported the idea that the overall relative risk of colorectal cancer is reduced in people taking long term aspirin.[4] Another meta-analysis of observational data confirmed a protective effect in oesophageal cancer and provided evidence of a relation with dose and duration of treatment, and other studies showed a beneficial effect in ovarian cancer.[4 5] How aspirin or other non-steroidal anti-inflammatory drugs produce this effect is not entirely clear, but the synthesis or activity of COX 2 is increased in many tumours, and inhibition could activate apoptotic mechanisms or suppress angiogenesis.[6] It has even been suggested that the link between diet and the prevention of colorectal cancer is attributable to the presence of salicylic acid in plant and vegetable foodstuffs.[7]

Evidence from longitudinal studies of long term users of non-steroidal anti-inflammatory drugs originally pointed to a reduced risk of Alzheimer's disease,[8] and these findings are supported by other, more recent data,[9] where an inverse relation was found between taking aspirin (and other non-steroidal anti-inflammatory drugs) and Alzheimer's disease, but not other forms of dementia. The mechanism is uncertain—Alzheimer's has an inflammatory component and therefore COX 2 may be the target, although other mechanisms have been suggested.[10]

BMJ 2003;327:572–3