PUBLIC CITIZEN/GLOBAL TRADE WATCH

Trade rules that would raise the cost of HIV medicines come under fire at a July rally in Washington DC.

PUBLIC HEALTH

Trade deal to curb generic-drug use

Tighter patent rules could raise drug costs in poor countries.

BY AMY MAXMEN

"Wanted," the notice reads, in an American old-west style font, "Negotiating text of the Trans-Pacific Partnership Agreement." The online advert invites visitors to contribute to a reward payable to the WikiLeaks website should it manage to expose the trade agreement. As *Nature* went to press, the reward stood at US$24,490.

The tactic, employed by the activist group Just Foreign Policy in Washington DC, may be extreme, but it reflects a broader unease over a negotiation process that the advert says "could affect the health and welfare of billions of people". At issue are industry-friendly rules governing drug patents that could be written into the final text of the Trans-Pacific Partnership Agreement (TPP). The provisions could boost drug development and profits for the pharmaceutical industry, but also curb the use of cheaper generic medicines in low- and middle-income nations.

"In many parts of the world, access to generic drugs means the difference between life and death," says US congressman Henry Waxman (Democrat, California). He is one of several US politicians voicing concern over the closed-door TPP negotiations and the influence that the pharmaceutical industry is thought to be exerting on the process through US trade representatives. With the latest round of talks set to begin on 6 September in Leesburg, Virginia, public-health advocates are expressing fears that the outcome will reduce access to medicines.

Besides the United States, ten Pacific countries representing 34% of US trade have so far agreed to join the TPP — Australia, New Zealand, Singapore, Malaysia, Brunei, Vietnam, Peru, Chile, Canada and Mexico. The agreement, which could come into effect as early as next year, spans several trade areas, meaning that some countries may be tempted to forgo access to generic drugs in exchange for better access to US markets in other industries.

According to previously leaked documents, the TPP looks likely to strengthen patent protection for drugs more than any trade agreement so far. Whereas the current World Trade Organization (WTO) agreement sets a minimum 20-year period for patents around the world, the TPP would follow US practice in extending patents beyond 20 years when the drug-approval process has delayed a drug's market entrance. Partner countries would also be pressed to award new patents for off-patent drugs that have been formulated in a new way or approved for a new set of patients.

This practice restricts access to medicines in poor countries because it extends patent monopolies. For example, according to Médecins Sans Frontières (also known as Doctors Without Borders) in Geneva, Switzerland, countries that have rejected patents on new formulations of the off-patent HIV drug Abacavir now sell generic versions for as little as $139 per person per year, whereas in Malaysia paediatric Abacavir costs $1,200 per child per year, because the country granted the new formulation a patent. But a spokesperson from the Office of the US Trade Representative says that patenting new formulations of old drugs provides an incentive for drug companies to develop adaptations "that are valued in developing countries, like heat-stabilized medicines for places without refrigeration".

Industry stakeholders say that drug companies need greater protection as the industry enters an unprecedented period of patent expirations (see *Nature* **480,** 16–17; 2011) and faces stiff competition from generics produced in India and China. They argue that sales of generics need to be restricted if companies are to recoup the millions they invest in developing new drugs. "If TPP countries wish to be those in which innovation flourishes, they should have strong intellectual property," says Stephen Ezell, senior analyst at the Information Technology and Innovation Foundation, a non-profit think tank in Washington DC that supports patent extensions.

The negotiators are considering special protections for biologic drugs — those based on large biological molecules. One possibility under discussion would grant companies a 12-year period of exclusivity on clinical-trial data related to the biologics they develop. Makers of equivalents of small-molecule drugs rely on such data when they seek government approval for their products. Without access to the data, the generics company would have to repeat the costly clinical trials or delay the time-consuming approval process for its product by 12 years. Charlene Barshefsky, a former US trade representative who now advises companies on trade law, explains that the biologics market, which was worth US$149 billion globally in 2010, needs extra protection because biologics cost more to develop than small-molecule drugs. "I am not saying that a foreign innovator cannot develop their own biologic drug, they just need to do their own homework," she says.

More generally, stronger patent provisions would harm small, domestic manufacturers of generic drugs in Malaysia and Vietnam, says Shawn Brown, formerly vice-president for international affairs and state government at the Generic Pharmaceutical Association based in Washington DC. They would also cut sales for larger generics manufacturers in the United

States, Australia and Canada that supply low-cost drugs to the world.

Some countries whose governments purchase drugs with a set budget are also alarmed by signs that the TPP may grant new negotiating powers to the industry. In New Zealand, for example, a government agency called Pharmac determines whether the benefits of a new drug warrant the cost, or if the country is better off sticking with a cheaper alternative. A leaked TPP provision would empower drug companies to appeal such decisions. "We have good processes for ensuring what is for the good of our population, not for the good of lobby groups, and I don't see why they need to interfere with that," says Marilyn Head, a policy analyst at the New Zealand Nurses Organisation in Wellington, who adds: "Bugger off, quite frankly." ■

CHEMISTRY

Electro-optic dye triggers ethics row

Dispute puts focus on reporting standards for major grants.

BY EUGENIE SAMUEL REICH

When a colleague questions a researcher's hypothesis, how far must the researcher go in telling his prospective funders about those doubts?

The question sits at the heart of a dispute that has prompted a government review of alleged omissions in reports from a science and technology centre funded by grants totalling US$36 million over 10 years from the National Science Foundation (NSF). The review, by the NSF's inspector general, is not yet complete, but the affair highlights a grey area in the agency's rules for grant recipients: although the rules require principal investigators to disclose any problems they encounter in pursuit of their research goals, they offer no guidance on how to assess when a colleague's scepticism about a specific issue merits reporting.

The issue became public in late July, when Bart Kahr, a chemist at New York University in New York city, described his side of the dispute at a meeting of the American Crystallographic Association in Boston, Massachusetts. But it goes back more than a decade, to work led by Larry Dalton at the University of Washington in Seattle in 2000. Motivated by the rapid expansion of the Internet, the group was developing modulators, colloquially called 'opto-chips', that convert electrical to optical signals, a more efficient medium for long-distance communication. Dalton and his team reported[1] record-breaking performances by electro-optic devices based on dye molecules they had designed. And their paper suggested that the key to the devices' performance lay in the way the molecules lined up in an electric field.

The result was discussed in a 2001 grant proposal to the NSF, which subsequently funded the Center on Materials and Devices for Information Technology Research at the University of Washington, with Dalton as its director. Research continued on the devices, and Kahr joined the centre in 2003. Several groups at the centre and elsewhere were continuing to report improved performances for the devices, but Kahr began to doubt the mechanism that had been proposed to explain how they worked.

Kahr obtained samples of dye molecules from another researcher at the centre, Alex Jen, and measured their absorption of polarized light — a way to test their alignment — in an electric field. Kahr reported to Jen that his results suggested there was no strong alignment and that future efforts to improve the devices by optimizing the dye alignment might not work unless the mechanism was understood. But the centre's annual report to the NSF for 2003–04 did not mention Kahr's findings. Jen, who wrote the relevant section, explains that he had a wealth of material to include, and that there was no effort to omit Kahr's results because they challenged an aspect of the centre's research direction.

Alarmed at what he regarded as an unethical omission, Kahr complained in 2004 to chemist Alvin Kwiram, then the centre's executive director. Kwiram says that Kahr's doubts were a distraction from the centre's main goal, which was to build and improve working devices. Although Kahr believed that understanding the mechanism was necessary to improve the devices as quickly as possible, Kwiram and others felt that they were already being made more effective even though the mechanism was in dispute. "This issue [of the mechanism] was like a mosquito buzzing around and it was like don't bite me right now when we've got bigger fish to fry," Kwiram says.

The centre submitted two more annual reports without mentioning Kahr's finding that the alignment was weak, and in 2006 the centre's grant came up for a five-year renewal. Phil Reid, a chemist at the centre who is now its director, says that during a site visit by NSF reviewers, Jen mentioned theoretical work suggesting that the dye molecules might not be aligned as strongly as supposed — work also mentioned in the 2005–06 annual report although not in connection with Kahr and his concerns. Kahr says that he did not have an opportunity to present his data to the NSF reviewers, and that he subsequently lost funding he had been receiving through the centre.

Kahr moved to New York University in 2009. In 2011, Reid, Jen, Dalton and Bruce Robinson, a theoretical chemist at the University of Washington, published a paper[2] presenting their own evidence that some dye molecules similar to those used in the original work align only weakly in an electric field — findings that paralleled those of Kahr. Robinson sees this simply as the resolution of a scientific disagreement, not a matter of research ethics. "Bart was right," says Robinson, "but so what?"

After receiving copies of Kahr's e-mails to centre members raising ethical concerns about the omissions, the University of Washington's Office of Scholarly Integrity and Ana Mari Cauce, dean of the university's College of Arts and Sciences at the time, conducted separate investigations of his allegations in 2010 and 2011. Both cleared Dalton and Jen — the only targets of Kahr's accusations — of any violation of ethics. Cauce, who is now the university's provost, explained in a letter to Kahr that Jen's omission of Kahr's data from the annual reports was justified because the data were preliminary and because there was a scientific disagreement about whether the molecules were aligned.

NSF rules offer no guidance on how to assess when a colleague's scepticism merits reporting.

But Kahr remained unsatisfied and in January 2011 submitted allegations to the NSF's Office of Inspector General. Susan Carnohan, a spokeswoman for the inspector general, told *Nature* that the office does not comment on ongoing investigations.

Jason Borenstein, a philosopher who teaches responsible conduct of research to science and engineering students at Georgia Institute of Technology in Atlanta, believes that grant applicants should generally disclose a colleague's doubts in their reports to funders. "Typically it is preferred, if there is space, to say there is another viewpoint that could be presented but we believe ours is right for the following reasons," he says. "That will make a better case to the grant reviewers." ■

1. Shi, Y. *et al. Science* **288,** 119–122 (2000).
2. Olbricht, B. C. *et al. J. Phys. Chem. B* **115,** 231–241 (2011).