WHO guidelines presage US biosimilars legislation?

As *Nature Biotechnology* went to press, the World Health Organization (WHO) in Geneva was finalizing a new set of guidelines for Similar Biotherapeutic Products. The WHO expects these draft guidelines, prepared by the Expert Committee on Biological Standardization, to be circulated to national regulators, manufacturers and other interested parties during 2010 and 2011. The guidelines, to which Keith Webber, deputy director of the Office of Pharmaceutical Science at the US Food and Drug Administration's (FDA's) Center for Drug Evaluation and Research contributed as a technical expert, come as the US prepares to draw up a long-awaited biogenerics pathway. But in the US, the debate over market exclusivity is threatening to divert the biosimilars discussion down an unproductive cul-de-sac, despite the introduction of bills for biosimilars legislation in the Senate (Senate HELP Health Care Reform bill) and the House of Representatives (HR 1548) during the summer.

When the US Congress enacted the US Drug Price Competition and Patent Term Restoration (Hatch-Waxman) Act 25 years ago, opening the way for the FDA to approve generic drugs, biologics were not included. Bill Haddad, chairman and CEO of Biogenerics in Brewster, New York, who was instrumental in initiating and negotiating the Hatch-Waxman Act takes that omission personally. "I made a big mistake 25 years ago," he says, "and it's time to make amends." He is working with generics industry lobby groups such as the Generic Pharmaceutical Association in Arlington, Virginia, to accelerate the passage of US legislation on biosimilars. "The stakes are high," says Haddad. "There are 25–30 [biologic] drugs out there with what amounts to perpetual patents." History demonstrates, he believes, just how profound an impact biosimilars legislation could have. "Thirty-five years ago, when we were first thinking about the legislation that became Hatch-Waxman, generic compounds had only 5% [by volume] of the US pharmaceuticals market: now they have 85%."

The impact of a biogeneric pathway, however, is unlikely to be as dramatic. In the first place, experience in the EU indicates that biosimilar-originator competition is not comparable with the direct substitution that occurs with small-molecule generics. The European Medicines Evaluation Agency's (EMEA's; London) approval pathway in 2005 has not triggered a deluge of biosimilars swamping existing markets. Some 12 products have been approved so far (**Table 1**) encompassing only three product classes (human growth hormone, erythropoietin (EPO) and granulocyte colony stimulating factor). Applications for follow-on insulin and interferon products have been refused or subsequently withdrawn.

According to Suzette Kox, senior director of Scientific Affairs at the European Generic Medicines Association in Brussels, the impact of biosimilars in Europe has not been profound. "There may be an overall 20–30% decrease in

WHO headquarters in Geneva. The WHO guidelines for similar biotherapeutic products have no political force but provide clear direction to member nations.

IN brief

Surprise ruling eases diagnostic makers' fears

Prometheus

Prometheus labs in San Diego

A federal court has ruled in favor of diagnostic test makers, after nearly a year of uncertainty over the patentability of medical diagnostic and treatment methods. In September the US Court of Appeals for the Federal Circuit in *Prometheus Labs Incorporated v Mayo Collaborative Services*, found that methods for analyzing the effect of a drug on a person can be patented. The eligibility of such patent claims had been in question since the Federal Circuit in October 2008 ruled in a case called *In Re Bilski* that only methods tied to a machine or those that transform something into a different state or thing are patentable. That standard, known as the 'machine-or-transformation' test, was set with business methods in mind, and appeared to exclude crucial aspects of diagnostics inventions. Diagnostics patents usually involve detecting molecules or biomarkers and correlating them with disease states–processes that might not pass this kind of machine-or-transformation test, says Stephen Albainy-Jenei, a patent attorney with Frost Brown Todd in Cincinnati, Ohio. "The *In Re Bilski* case really threw everything into doubt" for the pharmaceutical community, he says (*Nat. Biotechnol.* **27**, 586–587, 2009). But the Federal Circuit took a surprising turn in its recent *Prometheus* decision. The patents in question, held by Prometheus Labs in San Diego, cover a diagnostic test that enables doctors to determine levels of metabolites in patients who take thiopurine drugs, and adjust dosing accordingly. The method satisfies the 'transformation' prong of the test because the human body is transformed after administration of the drug and manipulated when the sample is taken, the court said. The decision provided some comfort to diagnostic patent holders, but more changes may lie ahead, says Edward Ramage, a patent attorney with Baker Donelson in Nashville, Tennessee. Next spring the US Supreme Court will hear an appeal of *In Re Bilski*. "The mere fact that they've [agreed to hear] *Bilski* means the machine-or-transformation test probably won't stand intact," he says. *Emily Waltz*

IN their words

"You can't win in this job. If you approve a drug, they accuse you of lowering standards. And if you don't approve it, you're the worst thing since the Nazi death camps." Richard Pazdur, the FDA's oncology chief, bemoans the sad lot of a regulator. (*New York Times*, September 16, 2009)