IN brief

Courts back Prometheus IP

In a ruling closely watched by developers of companion diagnostics, the US Court of Appeals for the Federal Circuit recently concluded that two methods for determining the optimal dosage of drugs to treat autoimmune diseases are patentable. The December 17, 2010, ruling reaffirmed the court's earlier decision in *Prometheus Labs. Inc. v. Mayo Collaborative Services.* Prometheus Laboratories of San Diego sued the Mayo Clinic for patent infringement when the medical group applied an in-house diagnostic test instead of sending samples to Prometheus. The Mayo Clinic claimed the process of giving a drug, observing its effects and adjusting the dosage is an abstract idea that was around before Prometheus patented the test. But the Federal Circuit upheld the patent. Then soon after the Supreme Court's *Bilski v. Kappos* decision (*Nat. Biotechnol.* **28**, 767, 2010), in which the court determined that the 'machine-or-transformation' test was only one of the considerations for an invention's patentability, it vacated the Federal Circuit's ruling and ordered the court to issue a new one. Prometheus argued the *Bilski* decision did not merit a reversal, as the tests "involve a particular transformation of a patient's body and bodily sample and use particular machines to determine metabolite concentrations in a bodily sample." The court came back with the same decision—good news for companies wanting to develop and patent companion diagnostic tests. *Michael Francisco*

Accelerated approvals examined

The US Food and Drug Administration (FDA) is seeking to improve the much-criticized accelerated approval program by reviewing six drugs approved under this pathway. The agency's Oncologic Drugs Advisory Committee (ODAC) held a meeting on February 8 to scrutinize Eli Lilly's Erbitux (cetuximab), GlaxoSmithKline's Bexxar (tositumomab) and Arranon (nelarabine); Genzyme's Clolar (clofarabine), Amgen's Vectibix (panitumumab) and Novartis' Gleevec (imatinib). The committee's intention was to analyze the process that brought these drugs to market without full confirmation that they are safe and effective. ODAC concluded that to grant accelerated approval, the agency should require a randomized trial, which could measure a surrogate endpoint. The panel also proposed that at the time of gaining accelerated approval, two randomized controlled trials should be under way. "The real issue is that lots of drugs are approved that are not terribly efficacious," argues Laurence Baker, chairman of the Southwest Oncology Group, Ann Arbor, Michigan, who was not on the panel. Recently, for instance, the agency withdrew the breast cancer indication for Avastin (bevacizumab), given accelerated approval in 2008, after studies found the drug did not provide a survival advantage (*Nat. Biotechnol.* **29**, 3–15, 2011). *Emma Dorey*

kind, the most common side effect is a cough, Pfeffer says. "We see less of that with the new inhaler in the small, early studies that we've done so far." Inhalers also produce a measurable reduction in lung function, though it is reversible and clinically insignificant. That side effect is also reduced with Dreamboat, he says. "It's kind of intuitive that inhaling less powder can't help but be a good thing."

If MannKind had gone to market with the earlier MedTone, "Bringing in a new inhaler would be very confusing," says Pfeffer, explaining why the company decided to swap as soon as the pivotal clinical trials had been completed.

Inhaled insulin has a checkered history. First developed in the mid-1990s, New York–based Pfizer's Exubera was the first inhaled insulin to receive FDA approval in 2006. Original estimates predicted $2 billion in sales, but the inhaler was unpopular with patients. Perhaps the biggest strike against it was the large, awkward delivery device—so ungainly it was nicknamed 'the bong'.

In addition, lingering uncertainty over a putative association between inhaled insulin and lung cancer also compromised patient uptake. The lukewarm reception for the product and poor sales prompted Pfizer to pull the product from the market only two years later, citing lung cancer concerns (*Nat. Biotechnol.* **26**, 479–480, 2008). Soon after, Novo Nordisk of Bagsvaerd, Denmark, also cancelled its phase 3 program for an inhaled insulin (*Nat. Biotechnol.* **26**, 255, 2008). "When you go and look at the original data, I don't know anybody who buys the argument that there was an increased lung cancer risk. The word on the street was that it wasn't selling and they needed an excuse to pull out of it," says Ananth Annapragada, a professor of entrepreneurial biomedical informatics and bioengineering at The University of Texas Health Science Center in Houston.

Inhaled insulin has clear advantages: it is simpler than injections and hypoglycemia incidents are sharply reduced, "which is probably the biggest fear of both doctors and patients regarding the use of injected insulin," says Pfeffer. Skyler also notes Afrezza's extremely fast action. Peak insulin is achieved at 14 minutes, compared with 49 minutes for Exubera. Rapid-acting insulin analogs like Novo Nordisk's Novolog, which peaks at 52 minutes, still don't become available rapidly enough to deal with the spike in glucose during a meal, Skyler says.

"[Afrezza] is the first really super-rapid-acting insulin. I think this will allow much better control. The second advantage is that the thumb-sized device makes it really easy to use. Those are two very attractive features that should resonate with patients and doctors," Skyler says. Afrezza could also ease concerns about potential effects on the lung. "This is so rapidly absorbed that there's little exposure in the lung. I don't think [safety] is an issue, but one never knows for sure. I think eventually it [will be] approved," says Skyler.

Although Afrezza is on hold, eyes are turning toward Generex of Toronto. The company's oral insulin Oral-lyn—an aerosolized, mixed-micelle liquid formulation, comprising recombinant insulin with excipients (alkali metal alkyl sulfate), absorption enhancers, phenol stabilizers and propellant—insulin spray is in phase 3 clinical trials. The product is delivered directly into the mouth and absorbed through the mucosa of the cheeks and the back of the throat. No product enters the lungs, according to the company.

Like Afrezza, Oralin is rapidly absorbed, with a dose taken immediately before eating, followed by a second dose after the meal. That profile mimics insulin patterns in nondiabetics, who experience an insulin peak 30 to 60 seconds after beginning to eat, says James Anderson, a professor at Indiana University in Bloomington, and a member of Generex's advisory board. "When you inject insulin, you don't get that large spike early on. [With Oral-lyn], you can get better control of the glucose rise following a meal than you can with injected insulin."

Overall, the reviews for MannKind and Generex are mixed. Clinicians still worry that insulin could be linked to lung cancer. "The long-term results of giving inhaled insulin are still not very clear. I think primary-care physicians will be reluctant to use it," says Joel Zonszein, director of the clinical diabetes center at Montefiore Medical Center, in the Bronx, New York, and a professor of clinical medicine at the Albert Einstein College of Medicine, also in the Bronx.

Also, improvements in injected insulin have eroded the need for alternatives. "The needles are not very painful—it's more painful to check blood sugar level. Patients don't complain much. If [Afrezza] is approved it will be a niche product but maybe a small niche for individuals who have needle phobia," says Zonszein.

But others still hold out hope that inhaled insulin can transform insulin therapy. "The reality is that superiority in efficacy is pretty much a given because of compliance. With injected insulin, compliance is terrible," says Annapragada. People are often reluctant to inject themselves in front of others, whereas Afrezza's Dreamboat is more like an asthma inhaler. "I don't know any [asthma sufferer] who won't take a puff in the middle of a meeting," he adds.

Jim Kling, ***Bellingham, Washington***