IN brief

Courts deny Pfizer access

JAMA editor-in-chief Catherine DeAngelis strongly backs the 'closed' nature of peer review.

The legal wrangle between New York-based Pfizer and three prominent medical journals over the release of confidential peer-review documents, the outcome of which directly affects biotech, ended with the integrity of the peer review process intact. Pfizer's demands to see confidential statements made on studies published by

the *New England Journal of Medicine* (NEJM) were rejected March 31. Lawyers for Pfizer argued the information might help in defending Celebrex (celecoxib) and Bextra (valdecoxib) in ongoing lawsuits. Two weeks earlier, in a similar case involving the *Journal of the American Medical Association* (JAMA) and the *Archives of Internal Medicine*, a federal judge also quashed Pfizer's motion. At issue is the sacrosanctity of peer review, as a "confidential closed system generates a different quality of review," says Catherine DeAngelis, editor-in-chief of JAMA. In essence, researchers are more honest—and presumably accurate—when protected by a cloak of anonymity. In addition, most reviewers are not paid and risk retaliation if their identities are exposed. Hence, if the peer review were to be "opened," few researchers would be likely to perform the task, DeAngelis says. For biotech, their researchers often publish data in peer-reviewed journals, and that review is an important validation tool for a company's potential product, not to mention that publishing is a powerful way to attract investment capital. More important, says Raymond Warrell, CEO and president of Genta, in Berkeley, New Jersey, is the impact of a peer-reviewed publication down the pipeline. "Publication in peer-reviewed journals is the most effective way of bringing attention to the benefits of your drug," he says. "Data on file that have not been peer-reviewed have no such import." DeAngelis agrees: "If a drug rep walks into a doctor's office and says that a drug had been tested and the study appeared in *NEJM* or *JAMA*, *Lancet*, *Nature* or *Science*, that is worth something. If they say, 'Well, it wasn't published anywhere,' meaning no one peer-reviewed it, no one is going to listen to them."

—Trisha Gura

IN their words

"It seems our ideas about how infliximab was working may not have been correct."

University of College London's Michael Ehrenstein on the finding that Centocor's (Malvern, Pennsylvania) anti-tumor necrosis factor α chimeric antibody can regenerate healthy regulatory T cells.

company said that its own mice and rat studies showed "no indications" of carcinogenicity. As *Nature Biotechnology* went to press, Hakan Edstrom, Mannkind president and CEO, said that Mannkind had not made any changes to its development plans.

The link to cancer is terrible news for inhaled insulin developers, but the field was in trouble before that, facing competition from numerous alternatives to traditional injection: fast-acting insulin analogs, insulin pens using disposable needles and insulin pumps installed with a catheter in the abdomen. Melbourne, Australia-based Phosphagenics has an insulin patch in phase 2 trials. "I think right now everything is getting [easier to use]," says Nadav Kidron, CEO of Oramed, which is developing an oral form of insulin.

That greater availability of alternative forms of insulin was likely the undoing of Exubera sales, says Jay Skyler, a professor of medicine at the University of Miami and the associate director of the Diabetes Research Institute, who has advised all of the companies in the field and played a major role in the development of Exubera. At the time that Pfizer began clinical studies in the mid-1990s, inhaled insulin looked like a sure winner because there wasn't much else out there. "It had been the Holy Grail forever to avoid injection," says Skyler.

But Pfizer never demonstrated that Exubera was an improvement over existing insulin dosing regimens. And patients and physicians were mistrustful of a novel delivery mechanism, says Kridel. "There was a whole body of treating clinicians who were concerned about the impact of putting insulin into the lungs. Nobody knew if it would be toxic in the long term if it's used chronically." The recent news from Pfizer would appear to validate that conservative stance.

When Novo got out of the game in January, it cited the fact that its AERx liquid aerosol system offered no advantage over existing pen devices, including its own FlexPen. Lilly soon followed, leaving Skyler to suggest that "diabetes is a franchise for Novo and Lilly, and they looked at [Pfizer's program] and said, 'We'd better protect ourselves—if they convert the market [to inhaled insulin], we'll lose our franchise.' My bet is they went into the field not because they particularly wanted to, but because they were taking a

defensive posture. When Pfizer bailed, there was no reason to stay in it."

Others think the decisions may have had something to do with new FDA guidelines for diabetes drugs, released in February, which might have meant Lilly needed to commit to post-approval studies for approval. Or Lilly may have been concerned about the larger regulatory picture, including potential litigation relating to toxicity issues.

Whatever the reason, Mannkind now stands in front. Its Technosphere is rapid acting in part because it delivers insulin in monomer form—unlike traditional insulin that is injected as a hexamer and must be broken down to dimers and then to monomers. Hexameric insulin hits its peak blood concentration 45 minutes to an hour after injection and it tails off gradually, residing in the blood for 8–10 hours. Technosphere

"Nobody knew if [inhaled insulin] would be toxic in the long term if it's used chronically."

delivers insulin using particles that dissolve instantly when they come in contact with lung tissue; the large surface area of the lungs plus the insulin monomer form

cause a peak concentration in about 15 minutes, and 80% of it is gone from the bloodstream in three hours, says Edstrom. That is very similar to the insulin profile in healthy individuals, he adds. However, the company has suspended partnership discussions until phase 3 data are published, because it feels a fair valuation for the program is unlikely in the current climate.

Through no fault of its own, the road has just gotten rougher for Mannkind. "It will be very difficult to find funding for these studies," says Avis L. Bridgers, project analyst for pharmaceuticals at Nerac in Tolland, Connecticut, a research and advisory firm. "What I don't know is whether they have pre-clinical data that gives them some hope of differentiating their product from the others. That might be enough to convince them to continue on, but that pot at the end of the rainbow" is now smaller.

Meanwhile, Mannkind's Edstrom maintains that the pharmacodynamic profile offered by Technosphere could position it as a leader. But when asked to reassess the situation after the news of lung cancer cases broke in early April, Kridel was unambiguous in his response: "It looks like the day of oral insulin is here," he said.

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