IN brief

Monsanto's alfalfa reaches Supreme Court

Bo Insogna/istockphoto

Alfalfa is one of the most important legumes in agriculture.

In April, the US Supreme Court will hear Monsanto's case for why it should be cleared to resume reselling Roundup Ready alfalfa seeds. The verdict, which is expected to affect the regulation of other biotech crops, including genetically modified (GM) sugar beets, could make it easier for GM crops to stay on the market, as it will no longer be possible to ban a crop, once approved, without a full hearing. Monsanto's GM alfalfa was approved by the United States Department of Agriculture (USDA, Washington, DC) in 2005, but the Center for Food Safety in February 2006 sued the USDA for not properly investigating the impact of the GM seeds on the environment. The United States District Court for the Northern District of California in 2007 banned the GM alfalfa seeds nationwide, pending a draft environmental impact statement (EIS) from the USDA. Monsanto appealed, and the case has now worked its way to the US Supreme Court. Peter McHugh, deputy general counsel at the Biotechnology Industry Organization (Washington, DC), says he disagreed with the process applied in the lower courts, adding that if Monsanto wins, in the future the farmers, growers and seed producers of agbio "will have an opportunity to have a full and fair evidentiary hearing before there's an injunction." In short, the ruling will determine whether a product can be banned without a hearing after it has been given the agency's blessing. Drew Kershen, a professor of law at the University of Oklahoma, says it's "important to set the standard when injunctions can be used, when the argument is that USDA's Animal and Plant Health Inspection Service (APHIS) needs to stop and prepare an EIS." If the Supreme Court overturns the ban on alfalfa, it would mean that producers and users of GM seeds facing an injunction do not need to stop selling and planting their GM crops immediately, if at all. Either way, the ruling should affect other agbiotech court cases, specifically a case due to begin in March, also filed by the Center for Food Safety, against Monsanto's GM sugar beets. There is more at stake where beets are concerned (*Nat. Biotechnol.* **27**, 970, 2009), because whereas Roundup Ready alfalfa seeds make up only 1% of the market, sugar beets were deregulated in 2005, and today 95% of sugar beets sold are from Roundup Ready GM seeds.

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intervention," explains Fazeli. This would have further weakened the significance of the study findings, and it is on this point that Ark is seeking to change the committee's mind. The firm believes it can demonstrate that investigator bias could not have been an important factor and so the analyses were probably statistically significant.

However, the data could be compromised by a much more fundamental problem, namely the small numbers treated. Only 119 patients received the therapy in the phase 3 trial, far fewer than would be accepted in a pivotal trial for any small-molecule drug.

"The crucial question is, has there been enough patient exposure?" says Robin Davison, analyst at Edison Investment Research in London. He suspects that the EMEA may be reluctant to authorize such a novel therapy based on no more than 300-plus patients in total, even for a condition with very short life expectancy.

"That must have been a factor, because Ark is pioneering a regulatory pathway here," he notes. "Regulators are faced with a fine balance, knowing that granting the first approval for gene therapy based on a relatively small exposure might open the door to similar approvals. That must be weighing on their minds—they may feel they may be opening Pandora's box." These issues are particularly acute for gene therapy products because of the field's checkered history in terms of clinical successes and media hype over adverse events. The death 11 years ago of a patient in an adenoviral gene therapy trial at the University of Pennsylvania (*Nat. Biotechnol.* **23**, 519–521, 2005) and more recent reports of toxicity in patients receiving adeno-associated virus (AAV) gene therapies (*Nat. Biotechnol.* **25**, 949, 2007) are likely to have attuned regulators to safety issues.

Companies with gene therapies in human trials, however, remain upbeat. Another European gene therapy company, Amsterdam Molecular Therapeutics (AMT) of Amsterdam, has filed a Marketing Authorization Application with EMEA for its lipoprotein lipase (LPL) deficiency treatment Glybera (a recombinant AAV vector expressing the Ser447X variant of the human LPL gene). "I cannot suspect any hidden agenda at the EMEA," says AMT chief executive officer Jörn Aldag. "We don't think the negative opinion has anything to do with gene therapy in general because EMEA's reasons are very clearly documented as benefit versus risk." The company is seeking approval for Glybera in Canada and expects to file in the US in 2012. The therapy could be available as early as next year.

An Ark spokesman says gene therapies, such as Cerepro, are "clearly" open for approval based on clinical results in the same way as established pharmaceuticals. The company notes that the Cerepro setback is "not entirely surprising," given the newness of the therapeutic approach and the notorious difficulties of trial designs around malignant glioma.

In fact, AMT's Aldag's perception is that gene therapy is seen increasingly by regulators as a favorable treatment mode: "The skepticism we have experienced in the past has actually declined." He says AMT was positively encouraged by regulators to file marketing applications for Glybera. Here again, however, numbers in the clinic are small—studies so far have involved 27 patients.

The EMEA's opinion of Cerepro could sway thinking the other side of the Atlantic. According to Fazeli at Piper Jaffray, US physicians have been viewing the European regulatory process for Cerepro with "intense interest." If EMEA approval occurs, this may be a "gating factor" for a US marketing deal, he says.

There is little doubt that the US Food & Drug Administration (FDA) is watching Europe's gene therapy licensing policy very closely. The FDA holds regular bimonthly discussions with the EMEA's Committee for Advanced Therapies, the body ultimately responsible for the negative opinion on Cerepro. And according to Martyn Ward, head of clinical trials at the UK's Medicines & Healthcare Products Regulatory Agency (MHRA), FDA officials have in the past taken their lead from Europe when granting permission for early stage gene therapy trials.

Companies in the business know that the FDA is hanging back and plan their regulatory strategy accordingly. "Ark wanted to get EMEA approval so as to force FDA to come to a position," says Edison's Robin Davison. "Once a gene therapy has been approved in Europe, the FDA would feel political and patient pressure to consider it," he says. "And they wouldn't be able to rewrite the rules [for a clinical study] from scratch." But now, he says, nobody knows what the prospects for FDA submission might be.

As *Nature Biotechnology* went to press, an announcement from EMEA on the re-examination of Cerepro data was imminent. But the prospects are sobering. In the past four years, only ~30–40% of appeals on EMEA decisions have been successful—Roche's successful appeal for Tarceva (erlotinib) in pancreatic cancer in December 2006 is a notable example. From that perspective, the odds of the first gene therapy getting a green light from Europe's regulators look slightly worse than those of flipping a coin.

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