IN brief

HIV drugs made in tobacco

Fraunhofer IME

The bioreactor room

Europe's first clinical trial to test a human monoclonal antibody (mAb) made in genetically modified tobacco plants has been given the go-ahead by UK regulators. The Medicines and Healthcare Products Regulatory Agency approved in late June Pharma-Planta's phase-1 clinical trial to test an anti-HIV type 1 protein applied as a vaginal microbicide to stop transmission of the virus between sexual partners. Pharma-Planta, a consortium of 39 academic principal investigators and industrial partners in Europe and Africa funded by the European Commission, launched the project in 2004 as part of the Sixth Framework Program. The partners' goal was to road test the regulatory pathway in Europe by taking a candidate plant-made biotherapeutic and moving it beyond proof-of-concept studies to clinical evaluation. The mAb, designated 2G12, neutralizes HIV by binding to its gp120 surface glycoprotein. If safe, the product will be tested for effectiveness in protecting users against HIV infection. While the clinical trial is conducted at the University of Surrey in the UK, 2G12 is being produced in specialized greenhouses at the Fraunhofer Institute for Molecular Biology and Applied Ecology in Aachen, Germany. The approval is a major milestone. "This is indeed a big step forward in Europe, where development was hampered because of concerns over foods and GMOs [genetically modified organisms]," says Charles Arntzen, a co-director at the Biodesign Institute of Arizona State University in Tempe and a leader in the development of plant-produced vaccines. Perhaps more importantly, Pharma-Planta's step forward could boost the entire field of plant-produced vaccines where a "lot of positive results and exciting things" are ongoing, according to Arntzen. For instance, three major US plant-based, protein production facilities are up and running, providing "abundant capacity," and presenting a challenge "to fill the pipeline with products to use that capacity." Prospects now are bright for meeting part of that challenge, with several vaccines—some for sexually transmitted diseases and others for virus-induced diarrheal diseases—moving forward. Additionally, the carrot cell–produced enzyme taliglucerase alfa for treating Gaucher disease, developed by Protalix BioTherapeutics of Carmiel, Israel, has completed phase 3 clinical trials and may soon be licensed as a "biobetter," Arntzen says. Plants are attractive bioreactors because they are inexpensive and provide a versatile expression system for recombinant protein. *Jeffrey L Fox*

called Adcetris the poster child for accelerated approvals, a sentiment echoed by Susan Ellenberg, associate dean for clinical research at the University of Pennsylvania's Perelman School of Medicine in Philadelphia, who did stints both at the NIH and the FDA. "When you have something like the Seattle Genetics [drug], where it looks like it's head and shoulders [above others], then everyone is comfortable and you want to do something to get it out quickly."

So why the accolades? According to Wilson, Adcetris scored highly on several components that the FDA looks for in accelerated approvals. First, the drug should be for a setting where no standard therapy exists. Whereas some therapies exist for lymphomas, those who relapse, roughly one-third of patients, have nothing to fall back on and often they are young, in their thirties or forties; ALCL has no effective therapies. Second, the pivotal clinical trial must be likely to predict clinical benefit. In the Adcetris trials, the clinical benefit was stunning, with >70% experiencing a response (75% of Hodgkin's patients; 86% of ALCL patients). In fact, the data were so good that Seattle Genetics asked for a regular, rather than accelerated, approval, which the FDA refused based on the lack of safety data. With only small single-arm trials involving a few hundred patients in total, safety could not be assured.

Seattle Genetics CEO Clay Siegall feels that the dust-up over FDA's refusing regular approval was much ado about nothing. Going for regular approval was done for his shareholders, to reduce oversight; for patients, he says there was really no difference between the two pathways. "We thought the data was compelling and there was no risk to the patients, and the confirmatory trials are the right trials to do. We would have done them anyway," he says.

But, despite recent successes, the accelerated approval pathway might still be considered a work in progress. An analysis done by Pazdur's group of accelerated approvals for oncology drugs granted between the programs' inception in December 1992 and July 2010 concludes that the pathway is working as intended—with 35 drugs in 47 new indications receiving accelerated approval and only three (as *Nature Biotechnology* goes to press, four now, counting Avastin) falling by the wayside. However, nearly half the drugs in the analysis (21/47 indications) have yet to convert to regular approval, mostly due to incomplete confirmatory trials (*J. Natl. Cancer Inst.* **103**, 636–644, 2011). The authors have calculated a mean time to approval of 4.7 years, which they say is an improvement over time in the regular pathway (not including those drugs that have not converted to regular approval, a number of which were granted accelerated approval over 10 years ago).

This interpretation of the data is disputed in an accompanying editorial in the same issue by Ellenberg, who says that the authors overstate the case, as the time savings they reported was the difference between the time to accelerated approval and the time to full approval (*Nat. Biotechnol.* **29**, 13–15, 2011). "The time to complete a study aimed at achieving regular approval from the start would likely be far shorter than the time under the current scenario," she wrote. Furthermore, the fact that the regular approval of nearly half the drugs approved in the pathway still hangs in the balance is problematic for several reasons. Patients are receiving drugs that could have safety issues, efficacy issues or both. And although FDA decisions aren't based on price, the fact is that some oncology drugs come at a high cost, presumably borne by the payors and patients, in some cases for decades before the drug achieves regular approval status, as pointed out by Merrill Goozner, healthcare analyst and columnist for *The Fiscal Times* (http://gooznews.com/?p=3126).

In hearings held in February, the FDA considered this problem and came up with a strategy, which involved starting with a randomized study with a clinically meaningful end point and basing the approval on a surrogate part way through, with the expectation of completing the study to ultimately get the end point. In principle, this might be an efficient approach, but Ellenberg is concerned that if the data with surrogates are promising enough, patients may be unwilling to stay in a study. This can be less of a problem when it's a brand-new agent that nobody can get except in a study, but could be problematic with existing drugs going after a new indication.

Pazdur says that the agency is aware of that problem, and thus allows the confirmatory trials to be in a different disease setting. "The advantage for the sponsor is not only do they meet their commitment, but also, if the studies are successful, they get a new indication. We think that we are actually moving the field forward." In the Seattle Genetics case, for example, whereas the completed trial was done with refractory Hodgkin's, the confirmatory studies will be a first-line study in combination with other therapies. Instead of ALCL, which is a small indication, the confirmatory trial will be for all CD30-positive lymphomas. "We're covering the landscape where doctors want to see the data," says Siegall.

The FDA is in a tough spot, Ellenberg admits. If a drug shows a clinical benefit, people say, why did it take us so long to get it approved? But, when it fails, people say, why the rush to approval? "If you're not being bashed from both sides, you're not doing your job," she says. But Siegall thinks that if you take the long view, sponsors of drugs should realize there is a pattern. "You have to have a compelling story. If you look back at the FDA's decision processes, there's always a window for extraordinary drugs."

Laura DeFrancesco *Senior Editor*