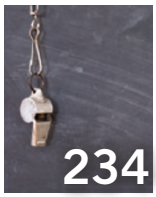
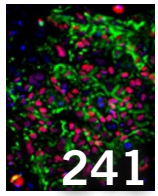


Strange silence:
Government scientists not afforded whistleblower protection

Massive goal:
Donna Ambrosino of MassBiologics on nonprofit drug manufacturing



Graft craft:
Skin disease provides testing bed for induced pluripotent stem cells

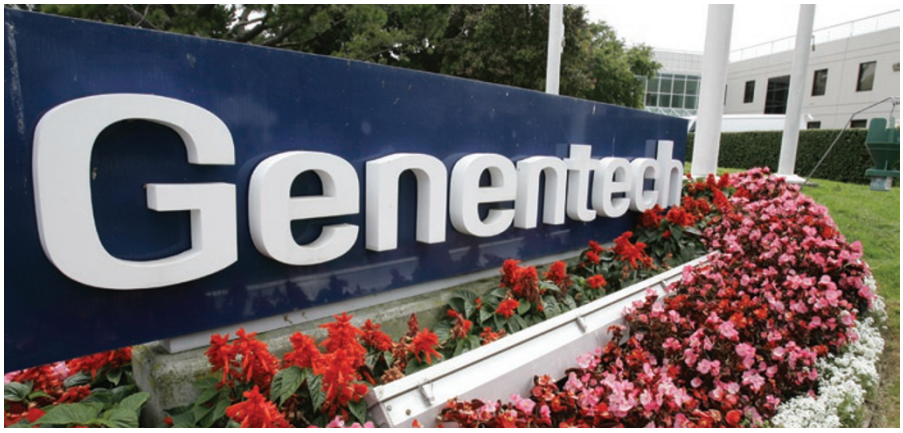
Fearful of Avastin's fate, Genentech asks for unusual hearing

The US Food and Drug Administration sent shockwaves through the medical community last year when it stated its plans to revoke marketing approval for the monoclonal antibody treatment Avastin (bevacizumab) in combination with the chemotherapy drug paclitaxel for first-line treatment of metastatic breast cancer. But rather than taking the blow sitting down, Genentech—which makes Avastin—is contesting the FDA's plans. The drugmaker's move, in the form of a 98-page petition submitted in January in support of its request for a public hearing, is unprecedented, and some analysts quietly worry it could jeopardize the goodwill between the company and regulators.

In its arguments to the FDA, Genentech, a South San Francisco–based unit of the Swiss pharma giant Roche, is keeping the debate focused on questions of science and proof of efficacy, rather than issues of access and reimbursement, according to Cole Werble of Prevision Policy, a health care policy analysis consultancy in Washington, DC. "Genentech is using the debate with the FDA to create a public record," he says. "It allows them to make the arguments for the oncology community to see." The FDA's regulations provide for public participation at a hearing, but a Genentech spokesperson told *Nature Medicine* in an email that it has no plans to ask patient advocacy groups or payers to present on its behalf.

The FDA gave Avastin the go-ahead for use in metastatic Her2-negative breast cancer in 2008 under its accelerated approval process based on a study showing a 5.5-month improvement in patients' median progression-free survival (*J. Clin. Oncol.* **27**, 4966–4972, 2009). Two subsequent trials examining Avastin with other types of chemotherapy showed a less striking improvement in this endpoint measure. That follow-up information led an FDA advisory committee to vote 12-1 last summer in favor of removing approval for Avastin's use in metastatic breast cancer, saying the drug's benefits did not outweigh its risks. Its approvals in other cancers are unaffected.

No pharmaceutical firm has ever asked for a hearing to challenge an FDA proposal to withdraw a single indication for a drug on the basis of data gathered as part of post-marketing commitments. That said, there have only been a handful of cases where the regulator has limited marketing authorization based on post-approval data. Pfizer voluntarily withdrew the leukemia drug Mylotarg (gemtuzumab ozogamicin) last year following a high death rate in a confirmatory trial conducted as part of its post-marketing commitments after accelerated approval. And in 2005, MedImmune decided to withdraw an indication for Ethyol (amifostine), its drug to reduce the side-effects of chemotherapy and radiation, just as the FDA was about to review post-marketing study data on Ethyol's use in non-small cell lung cancer.



AP Photo/Paul Sakuma

Blossoming hopes: Will a public hearing sway regulators to soften their stance on the cancer drug?

There's much more at stake for Genentech. Avastin is a blockbuster drug with 2010 revenues of 6.5 billion Swiss francs ($6.7 billion), up 9% from the prior year. However, "the breast cancer discussions with the FDA had an impact on our sales in the United States in 2010," Roche chief executive Severin Schwan told investors on a recent earnings call. "We expect further decline in 2011," he said, prompting the company to cut its 2011 forecast for Avastin from 8–9 billion Swiss francs to around 7 billion.

First-line defense

In its petition, Genentech claims that the improvement in progression-free survival in its original study "is not invalidated by the two subsequent studies with alternative Avastin-chemotherapy combinations." It also says the proposed withdrawal reflects a new approval standard for the first-line treatment of metastatic breast cancer that "will be difficult for novel therapies to meet in the future." The company has offered to conduct a new trial of Avastin while maintaining the indication.

Multiple patient advocacy groups, for breast as well as other cancer types, expressed concern that the FDA's action would delay or curtail access to potentially life-saving drugs.

"We want good drugs to come to market as quickly as possible," says Cara Tenenbaum, vice president of policy and external affairs for the Ovarian Cancer National Alliance. But, she adds, "if I were a company, I'd be a little nervous about an accelerated approval."

Tim Turnham, executive director of the Melanoma Research Foundation, says Genentech deserves an explanation for the FDA's change of heart. "My support for having a hearing is simply to say, the company had one understanding and it changed. At least give them a chance to address that."

Whenever it proposes to withdraw an indication for a drug, the FDA also provides a notice of an opportunity to petition for a public hearing, but whether it will grant one in this case is unknown. Either way, for a company to "force the agency to make a strong, difficult public defense of its decisions—especially in a visible and highly sensitive area like breast cancer treatment" is risky, says Werble.

Mark Ratner