Health Beat
by Maggie Mahar

WALL STREET, CANCER, AND THE FDA: A CAUTIONARY TALE

Only in America do physicians who evaluate new drugs need bodyguards.

You may have read about the brouhaha surrounding Provenge, a vaccine designed to extend the lives of men suffering from late-stage prostate cancer. In March, a Food and Drug Administration (FDA) advisory panel voted 13 to 4 to recommend approval. The next day, shares of Dendreon, the drug's sponsor, doubled.

But shareholders did not celebrate for long. Two of the dissenting votes were cast by the panel's two prostate cancer specialists: Sloan-Kettering's Howard Scher and the University of Michigan's Maha Hussain. And they did not just vote "no"—following the hearing, both wrote to the FDA arguing that Dendreon offered no solid evidence that Provenge works.

The FDA listened. And in May it told the company it wouldn't approve the drug until it had more data. That is when the two oncologists began receiving threatening e-mails, phone calls, and letters. Many were anonymous.

No doubt much of the hate mail came from investors who had watched Dendreon's shares climb from $5 in early January to $25.25 in late March—before plunging to $3 and change. One Alabama shareholder expressed his feelings on his MySpace page, where he asks "Hey, Hey, FDA, How Many Dads Did You Kill Today?" while images of Hussain and Scher flash across a backdrop of crooked crosses. Mozart's "Requiem" plays in the background.

The response illustrates how, in a money-driven health care system, those who view health care as a profit center strive to dictate social policy. From their point of view, the FDA should approve any product that Wall Street finds attractive—and then let the market decide whether or not the drug is both safe and effective. What they ignore is that, unlike other consumers, sick patients are not in a good position to comparison-shop. They must rely on the doctors and scientists who serve on FDA panels to sort through the hundreds of offerings that drug makers hope to bring to market. For even if a drug makes it to Phase III trials, this is no assurance that it is safe—or that it will work. Indeed, a recent study shows that fully 40 percent of new drugs fail in that final stage of testing.

HEADQUARTERS: 41 EAST 70TH STREET – NEW YORK, NY 10021 – 212.535.4441 – 212.535.7534 (FAX) – INFO@TCF.ORG – WWW.TCF.ORG
D.C. OFFICE: 1333 H STREET, NW – 10TH FLOOR – WASHINGTON, D.C. 20005 – 202.387.0400 – 202.483.9430 (FAX) – INFO@TCF.ORG – WWW.TCF.ORG

So far, the FDA has not bowed to investor pressure regarding Provenge, but the e-mails and phone calls were too menacing to be ignored. When Hussain and Scher attended the conference of the American Society of Clinical Oncology last month, both asked for extra security guards. At that point, Hussain began wondering whether she should continue as an FDA adviser.

Patients also protested the FDA's decision. Many had pinned their hopes on Provenge because it is one of a group of new cancer drugs under development that uses the patient's own cells to create a vaccine designed to mobilize the patient's immune system to attack the cancer. The notion that the body might "heal itself" is enormously seductive. For more than a century, oncologists have dreamed of such a solution. But thus far, as Dr. Steven A. Rosenberg of the National Cancer Institute confirmed in an e-mail to me last week, "there are no therapeutic vaccines that have been shown to be effective."

This is not what patients want to hear. But while many were crushed by the FDA's decision, patient advocates such as PSA Rising disown the hate mail. "Folks, this is not *grassroots* cancer patient activity, it's . . . naked grassroots investor activity," wrote Jaqueline Strax, the editor of PSA Rising, in her newsletter for prostate cancer survivors. "Ironically, some investors have whined that prostate cancer patients are not helping THEM on behalf of Dendreon."

Meanwhile, shareholders charged that Sloane-Kettering's Scher nixed the drug because he is the lead investigator for a rival product. To drive this point home, earlier this month Provenge activists raised $24,000 on the Dendreon message board at Investor Village to buy a half-page ad in the *Washington Post* headlined "Prostate Cancer Victims Face Needless Suffering and Premature Death."

Could this be true? Knowing how much misinformation swirls around any new cancer drug, I decided to take a close look at the transcript of the FDA hearing and find out more about the scientific evidence behind Provenge.

This is when my skepticism turned to shock. First, I learned that Dendreon has done two clinical trials attempting to show that Provenge slows the progress of the cancer. And that both failed. That's right—the studies offered absolutely no proof that the drug put a brake on the disease.

"It's not clear why the FDA panel was even voting on the drug—Provenge had already been check-mated," says Paul Goldberg, who broke the story by printing Scher's letter to the FDA in *The Cancer Letter*, a weekly newsletter about the politics of cancer.

But Dendreon persisted. Undeterred by the failed trials, the company went back and found another way to slice and dice the numbers. It turns out that in a small trial of 172 men, the group who received Provenge lived an average of 4½ months longer than those who received the placebo. There was, however, no scientific evidence that they lived longer *because* they received Provenge.

As Mario Sznol, a medical oncologist at Yale points out, "A lot of these trials of cancer [drugs like Provenge] are small, and their response rates are low. That means some positive findings could simply be due to chance."

At the hearing Hussain also pointed out that there was no data showing that Provenge slowed the development of pain. Asked about quality of life during those extra 4½ months, the company replied: "We didn't study that."

Of course they didn't. When late-stage prostate cancer spreads, patients can experience severe bone pain.

Moreover, although the panel voted unanimously that Provenge appeared "reasonably safe," nearly 5 percent of the men given Provenge suffered a stroke, versus 1.7 percent of those who received the placebo. In a trial of 172, this, too, could be chance. But at the hearing, even the panel's industry representative found the statistic troubling: "I think clearly the product is safe except for the issue of CVA (cardiovascular accident)" he said. "That clearly bears watching . . . . I'm sure the company would be willing to watch that carefully in post-marketing."

Great. Wait until after the drug is on the market—and *then* find out whether it offers any benefit, and whether the risk of stroke is so great that it outweighs the possible (though unproven) benefit.

With all this damning evidence against Provenge, why, in the end, did so many of the panelists vote yes? The transcript demonstrates how easily one person can turn the tide at an FDA hearing.

At first, the panel seemed on its way to denying approval. As Goldberg points out in *The Cancer Letter,* three committee members in a row had voted "no," saying that the data failed to "establish the efficacy" of Provenge, when Celia Witten, the director of the FDA Office of Cellular, Tissue and Gene Therapies, jumped in to rephrase the question:

"The question we are really asking [is] 'Do you believe that this product works, that it's efficacious?' . . . That's really what we are asking. If somehow some of the words are not clear . . . the regulatory definition is 'provide[s] substantial evidence.' So that's our standard. Is there substantial evidence that it works?"

It was as if Witten had cued the panel. "Yes, there is substantial evidence," said one panel member, switching his vote—though, clearly, he still was not sure.

Suddenly, the question seemed less a matter of science than semantics. Not everyone was confused by the change in wording, however. Maha Hussain replied vigorously: "To me, 'substantial' and 'established' are the same, and 'No' to both." But most of the panel fell into line.

"The FDA can shape the outcome of a panel meeting by how they pose the question," observes Adam Feuerstein, who follows Provenge for TheStreet.com and watched a Web-cast of the hearing. "It was clear that they were going against the drug, and then, suddenly, they flipped. I thought 'Whoa.'" (Feuerstein, who has taken a skeptical view of the stock, also has received what he describes as "nasty, sometimes anti-Semitic e-mails.")

But returning to the plight of dying patients, even if the panel was wrong to recommend immediate approval, shouldn't individual patients have a right to gamble on the drug?

This is the question The Abigail Alliance asks. In 2003, the Alliance, which commemorates Abigail Burroughs, a twenty-one-year-old who died of cancer after trying, unsuccessfully, to gain access to a drug called Erbitux, sued the FDA. A lower court dismissed the suit, but last spring, a three-judge appellate panel in the District of Columbia endorsed the group's claims.

Some oncologists warn that the ruling could undermine the whole drug-evaluation system. After all, if patients have direct access to experimental and unproven drugs, how do you convince any of them to enter a randomized, controlled trial where perhaps half will receive a placebo? And without such carefully controlled trials, how can researchers ever know whether a drug is both safe and effective?

One cannot help but think of the many breast cancer patients who were subjected to painful bone marrow transplants before a randomized clinical trial showed that the transplants did no good. In the late 1980s and early 1990s, the media had trumpeted news of the experimental treatment, and pressure from patients, state legislatures, and courts forced insurers to begin paying for the procedure. Meanwhile, large, government-funded randomized studies that were designed to evaluate the effectiveness of the transplants experienced significant delays because, since more than 20,000 women were able to get the transplants outside of the trials, it took years to enroll just 1,000 women to complete the research.

Ultimately the randomized trial showed that the procedure was no more helpful than regular chemotherapy—though it was more dangerous, debilitating, and expensive. "The women got so sick, they couldn't raise their heads. It's so horrible and so hard, and you don't have time to say good-bye to the people you love," recalled attorney Alice Phillipson, referring to the women whom she represented in suits against HMOs. Ultimately, she stopped taking the cases.

By the time the results of the trial were known, the nation had squandered roughly $3 billion on the therapy, while an estimated 4,000 to 9,000 women died, not from their cancer, but from the supposed cure.

Even Frank Burroughs, Abigail's father and the president of The Abigail Alliance, recognizes the importance of randomized trials. Earlier this month, he suggested that "regulations . . . be drafted to require patients to apply to clinical trials first, before seeking to purchase [an experimental] drug."

In fact, Dendreon already is running a large, randomized controlled trial specifically designed to test whether those who receive Provenge do, indeed, live longer. Dendreon hopes to enroll 500 patients in the trial—at last report it had filled just 425 slots, which means that patients who qualify may still be able to get access to the drug. (If the FDA had approved Provenge last May, it would have been very difficult to find the 75 patients needed to round out the study.)

But after all of the publicity suggesting that Provenge "saves lives," will patients be willing to enter a trial in which they risk receiving the placebo? Yes, if their doctors look at the data and tell them the truth: "Today we really don't knows whether Provenge will do you any good. The only way to find out is if enough people sign up for the trial."

Scher and Hussain believe the FDA should wait for the results from this larger trial. Interim data will be available in the middle or second half of next year.

Hussain has suggested that, in the meantime, Dendreon could make the drug available to dying patients "for compassionate use." But Dendreon CEO Mitchell Gold has said, "No, the company does not have that kind of resources." Though, *The Cancer Letter*'s Goldberg points out, under the compassionate use rubric there is a mechanism for the company to recover the cost of the drug. But it wouldn't be able to turn a profit.

By contrast, if and when the FDA ultimately approves the drug, Wall Street analysts estimate that the company could rake in as much as $1 billion in worldwide sales. (This calculation is based on the not-unreasonable assumption that Provenge will be able to charge $60,000 per patient.)

This raises another question: Is a drug that might, at best, give the average patient an extra 4½ months of (perhaps very painful) life worth $60,000? Unfortunately, at this point in time, the FDA is not allowed to talk about cost-effectiveness and Medicare is not allowed negotiate prices based on a drug's value.

This is why FDA approval is such a hot button for investors: they know that once a drug gets the nod from the FDA, Medicare will almost certainly cover it, and many insurers will feel obliged to follow suit (passing the cost on to all of us in the form of higher premiums). And at that point, the company can charge virtually any amount that it chooses. As Morgan Stanley analyst Dr. Steven Harr told the *Wall Street Journal* a few months ago, when it comes to cancer drugs the "market . . . effectively provides no mechanism for price control . . . other than [the] companies' goodwill and tolerance for adverse publicity." (So far, most companies have proved stoic in the face of adverse publicity; thanks in large part to spiraling prices, cancer drugs now account for 22 percent of the nation's spending on drugs. Though Harr warns that at some point, the government will push back and begin putting a cap on prices.)

In the meantime, "the stock has become the momentum trading vehicle of 2007," TheStreet.com's Adam Feuerstein wrote earlier this month. "A stock that will be pumped and dumped based on the flimsiest of rumors and lowest-common denominator reporting."

Inevitably, the Wall Street hype spills over into the mainstream media, where dying patients, willing to grab at any thread of hope, read about a drug and begin to believe that, if they could just get access to the "newest new thing," it might save their lives. (In fact, even the company claims only that the average patient *might* win an extra 4½ months.) Those who "pump" the stock do patients a cruel disservice.

In all of this, the FDA is not without blame. The fact that it continues to let physicians, like Scher, who can be accused of financial conflict of interest serve on its panels only further muddies the waters. In the end, it seems that Scher had good reason to vote against recommending immediate approval. "I think the conflict of interest charge is a total red herring," says Feuerstein. Nevertheless, when it comes to patients' confidence in the FDA's decisions, the perception of conflict of interest can be as important as the reality. The agency has promised that it will tighten conflict of interest rules for panel members, but so far has not fulfilled the pledge—though the House of Representatives has passed a bill that would permit only one person with a financial conflict on a FDA panel.

Finally, the Provenge saga demonstrates how, in our profit-driven health care system, the quest for profits can have a chilling effect on the rational discourse and informed reporting needed to pave the way for evidence-based medicine. For Scher and Hussain were not the only ones intimated by investors' threats.

Even Dr. Leonard Lichtenfeld, Deputy Chief Medical Officer for the American Cancer Society and author of "Dr. Len's Cancer Blog," acknowledges that he was alarmed when he heard about the ugly messages that Hussain and Scher had received.

"I did something the other day that has bothered me for the past 72 hours: I decided not to publish a comment because of fear of retribution or possibly retaliation," Lichtenfeld admitted on his blog last month.

"Today, I decided to correct that decision and discuss my concerns, Lichtenfeld wrote, and went on to declare that "my personal opinion based on the information I have read is that it is appropriate to await the results of the current clinical trial to determine whether or not in fact Provenge improves survival in advanced prostate cancer."

Lichtenfed explained that he decided not to write about Provenge after hearing about the threats while en route to the American Society of Clinical Onocology (ASCO) conference: "Because of the risk, I decided not to say anything publicly. Although I had written my blog on this topic, I edited the comments regarding Provenge out of the final posting."

When he got to the meeting, Lichtenfeld did, however, speak privately to some reporters, and he revealed "a common theme emerged. . . . They, too, had become reluctant to cover the story because of fear of retaliation. One reporter said that in his opinion you had to 'steel yourself' if you intended to report an opinion or comment in support of the FDA's conclusion."

"Frankly," Lichtenfeld confided, "this troubles me a great deal."

As well it should. If physicians, scientists and reporters are afraid to speak out about the FDA's decisions, then we can never hope to lay the groundwork for "evidence-based medicine"—health care based on the best scientific data available. Instead, we will continue to be vulnerable to the hype that raises false hopes, in a system where drug-makers and investors have far too much influence over what we know—or think we know—about the drugs we take.

If you would like to comment on this issue, please go to http://www.thehealthcareblog.com, where I have written a shorter post on this topic, with room for comments at the end.

WRITTEN BY MAGGIE MAHAR, A HEALTH CARE FELLOW AT THE CENTURY FOUNDATION AND THE AUTHOR OF *MONEY-DRIVEN MEDICINE: THE REAL REASON HEALTH CARE COSTS SO MUCH* (HARPER/COLLINS 2006)

JULY 12, 2007