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What went wrong at Aveo Pharmaceuticals - Business

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It took Aveo Pharmaceuticals Inc. seven years to develop a much anticipated kidney cancer drug. Federal regulators needed only about four hours to crush the company's hopes.

The Cambridge biotech's executives were brimming with confidence when they arrived for a Food and Drug Administration advisory committee meeting May 2 in Silver Spring, Md. The panel was expected to recommend that the drug — known as tivozanib — be approved for sale. Instead, Aveo's leaders endured a gut-wrenching morning, starting with the first speaker.

Clinical trial results showed "a concerning increase in the risk of death" from tivozanib, said Amna Ibrahim, deputy director of the agency's division of oncology products.

The session only got worse. A parade of officials questioned Aveo's data, criticized the trial design, and complained it was difficult — if not impossible — to interpret the findings. The grousing culminated with the FDA's influential oncology chief, Richard Pazdur, pronouncing Aveo's research "bothersome" and "confounding."

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Advisers that day voted 13-to-1 against recommending the drug be approved for sale. Six weeks later, the FDA formally rejected it.

Now Aveo is grappling with the fallout from the FDA's rejection as the company's shares have lost more than 70 percent of their value. Aveo scrapped its kidney cancer program and laid off 140 workers, 62 percent of the staff. Chief executive Tuan Ha-Ngoc apologized to patients, employees, and investors. Shareowners filed lawsuits — alleging the company issued misleading statements about tivozanib — and the Securities and Exchange Commission subpoenaed documents relating to the drug.

Aveo's failure dramatically illustrates the risky nature of biotechnology, a business built around lofty expectations and expensive research. The rewards can be huge — life-extending therapies for patients and financial bonanzas for investors. But more often, years of drug development and the drawn-out approval process ultimately lead nowhere.

While such outcomes are disappointing for companies, they can be devastating for those desperate to try new medicines that might defeat or stave off a fatal disease. The reality is that while officials and executives wrangle over scientific interpretations of studies and striking a balance between effectiveness and risk, people die. The form of kidney cancer Aveo's drug was designed to treat — renal cell carcinoma — kills more than 10,000 Americans each year, according to the National Cancer Institute.

"There were so many things that went wrong," said Dena Battle, a patient advocate who monitored the review. The drug "was a very effective treatment for kidney cancer patients," she said, "but it won't be approved to treat kidney cancer."

A transcript of the FDA hearing provides a look into a process that is — at best — opaque to most people. Because the agency typically won't approve a new drug unless it is at least as effective and safe as treatments already on the market, most fail long before getting to an advisory committee. Even a medicine that looks like a sure thing can be derailed.

Aveo, spun out of Dana-Farber Cancer Institute labs in 2002, spent more than $300 million to develop tivozanib after acquiring the compound from a Japanese research firm.

Company executives declined to be interviewed for this story. In written responses to questions, they said Aveo has two years' worth of cash on hand and is moving ahead with developing drugs — including tivozanib — to treat other types of cancer. "Aveo is looking forward," chief financial officer David B. Johnston wrote. The company will "vigorously defend against the class-action suits" and is cooperating with the SEC's inquiry, he said.

FDA and SEC representatives said they could not discuss their dealings with Aveo.

Like many other biotechs, Aveo began with a commitment to cutting-edge research and an adaptable business model.

The initial idea was to develop models in mice that could predict how cancer therapies might work in humans. But that changed in 2006 when its scientists identified a drug compound in the labs of the Japanese research firm Kyowa Hakko Kirin Co. that starved tumors by targeting the receptors that help them grow.

Aveo licensed the commercial rights to the compound — tivozanib — outside Asia. The move helped the company sell its stock on the public markets, raising $81 million in a 2010 initial public offering. The following year, Aveo struck a cost-sharing partnership with another Japanese firm, Astellas Pharma Inc., under which Aveo would apply for US approval of tivozanib, while Astellas wouldtackle the European market.

Results from early and mid-stage clinical trials looked promising. A 2012 article in the Journal of Clinical Oncology said tivozanib was effective in slowing the progress of renal cell carcinoma.

Then came the critical late-stage trial, which tested the effectiveness and safety of the drug on 517 patients. While updates from Aveo and Astellas seemed to show the program moving inexorably toward approval, the FDA hearing transcript sheds light on choices made during the trial design that muddled the process.

The first sign of trouble surfaced last summer when Aveo indicated in a regulatory filing that FDA officials had “expressed concern” about data from the late-stage trial.

To win approval of tivozanib, Aveo had to meet a primary goal — agreed to by the company and the FDA — of showing that it slowed the advance of kidney cancer more than a drug already for sale. While it achieved that goal, it fell short of a secondary goal: improving “overall survival” in comparison with the existing medicine, called Nexavar. Put another way, patients who took the existing drug during the trial lived longer than those using Aveo’s.

Regulators urged Aveo to conduct a second trial. But more testing would have been expensive and might have delayed approval for at least another year, so the company decided against it.

Senior biotechnology analyst Brian Klein, vice president at investment research firm Stifel, Nicolaus & Co. in New York, said company executives “felt they could explain away” FDA questions about why their drug didn’t seem to help patients live longer.

At the advisory meeting, Aveo’s chief medical officer, William Slichenmyer, spelled out the reasoning. Because of humanitarian concerns, he said, Aveo designed the trial to permit patients who were given Nexavarto to switch to tivozanib when their conditions worsened. That meant the deaths of some patients who made the switch were attributed to tivozanib when calculating survival rates. Slichenmyer contended that made Aveo’s drug look less effective.

While “crossovers” from one drug to another are common in clinical trials, trial sponsors typically allow patients taking an experimental drug to switch to the approved drug. By reversing that playbook, Aveo demonstrated confidence in its treatment — but also set itself up for problems.

FDA officials didn’t buy Aveo’s explanation. Even with knowledge of the crossover, regulators said the data were unclear, making the trial findings “uninterpretable when making a risk-benefit assessment necessary for approval of a drug.”

Another issue bothered regulators. They complained that too many patients from central and eastern European countries — where there are fewer cancer drugs and it is easier to enroll patients in trials — made the testing tougher to evaluate. Those patients made up 88 percent of participants in the trial, compared with only 8 percent from the United States.

“With this small number of patients” from the United States and Western Europe, “we cannot draw firm conclusions concerning regional differences,” said J. Dawn Arrington, an FDA medical officer.

Critics were outraged by the FDA’s position. By first allowing Aveo to use one benchmark for success, and then punishing it for not meeting a different standard, the agency unfairly “changed the rules,” according to patient advocate Battle. She and her husband, Chris, who has kidney cancer but has not taken tivozanib, argued before the advisory board that patients need more treatment options.

“This was not putting the patients first,” Battle said of the review process. “There will be repercussions that will be disturbing for drug development. Companies will look at this and wonder if they want to go forward with new cancer drugs.”

To those suffering from renal cell carcinoma, the disagreements between the FDA and Aveo over how the testing was conducted were exasperating. After all, many medical specialists did — and still do — believe Aveo’s drug works. But with the trials over and approval to sell it denied, people with the disease could no longer get the treatment. Chris Rees, an investor who lost money on Aveo, wrote on the financial website Seeking Alpha that “Tivozanib is now probably the best cancer drug the FDA won’t let cancer patients have.”

But other agency watchers say the FDA should not be blamed for Aveo’s failings.

Klein, from Stifel, Nicolaus, said Aveo mismanaged the clinical trial and ignored guidance from FDA officials, including the request for more testing.

“A lot of it has to do with hubris,” Klein said. “They were so confident that their drug was superior that they disregarded the advice of the agency that was regulating them. The real victims here are the patients. If the trial was conducted differently, the result might have been favorable.”

After the advisory vote, Aveo’s partner, Astellas, stopped funding the drug’s development in Europe. With its money cut off, and new investors unlikely to come knocking , the fate of Aveo’s kidney cancer program was sealed.

Despite the massive setback, Aveo remains open for business in Cambridge. Ha-Ngoc, Slichenmyer, and other top executives are still at their posts, overseeing a drastically smaller workforce.

What happens next is uncertain. Aveo and Astellas are testing tivozanib as a treatment for breast and colorectal cancers. But even under a best-case scenario, tivozanib and the other drug candidates Aveo is developing won’t be available to fight cancer for a long time. Unfortunately, for many of the patients who thought they were close to getting a drug that would improve and extend their lives, it might as well be never.