

FDA Blocked Melanoma Drug as Confusion Reigns Under Makary

In the industries regulated by the FDA, ranging from gene therapy to vaccines and cancer, officials are frustrated by the agency's uncertain direction.

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The FDA's [recent decision](#) to withhold approval of a new skin cancer treatment fell like a hammer on doctors who treat melanoma and patients who saw that the drug had prolonged the lives of a third of the participants in a clinical trial.

"It was devastating news," said Trisha Wise-Draper, a dermatologist at the University of Cincinnati who had patients enrolled in the trial.

"This is life or death for maybe 2,000 patients," added Eric Whitman, medical director of the Atlantic Health System's oncology service. A [Wall Street Journal editorial](#) assailed the ruling, noting that it "will have a chilling effect on drug development."

Despite the benefit to some patients, oncologists and pharmaceutical industry analysts say there were legitimate concerns about the treatment, called RP1, that may have led the FDA to reject it in any event. The company, they noted, had ignored repeated FDA suggestions that it change the design of the trial used to seek approval for the medication.

The FDA's decision would have raised few eyebrows before the current administration took power. But Marty Makary, who took charge as commissioner 13 months ago, altered the agency's culture and damaged the trust it had built over decades while regulating 20% of U.S. consumer spending, said Steven Grossman, a regulatory consultant and former Health and Human Services official.

"People have to speculate about the standards and processes by which the agency makes decisions," he said. "And that uncertainty is bad for everybody — patients and sponsors and investors."

Under Makary — who resigned [May 12] — senior officials have [either suppressed](#) or [pushed forward](#) some [drug approvals and policies](#) at the behest of President Donald Trump or HHS Secretary Robert F. Kennedy Jr., ignoring the advice of agency professionals. In defending his actions, Makary often eschewed the agency's traditionally measured language about its decisions.

In response to criticism for rejecting the melanoma treatment, for example, Makary accused its manufacturer, Replimune, of “corruption,” saying it was “engaging in corporate spin” to make the FDA look bad.

“I don’t work for Replimune. I work for the American people,” Makary said in a May 5 interview on CNBC. Kennedy backed him up during a congressional budget hearing in which Kennedy mistakenly claimed that patients in Replimune’s clinical trial had also received chemotherapy.

Makary did not respond to requests for comment.

“All the norms have been thrown out the window, so we don’t know what underlines an agency decision,” said [Paul Kim](#), a former FDA staffer and Senate aide to Sen. Edward Kennedy who’s now a pharmaceutical industry consultant in Boston. “Even when there are legitimate scientific and regulatory reasons why a drug will not be approved, we’re left guessing whether it’s legitimate grounds or just a political play.”

A Doomed Cancer Drug

Melanoma is the fifth most commonly diagnosed cancer in the United States, with about 112,000 new cases each year. The American Cancer Society projects that [about 8,500 people will die](#) from melanoma this year in the U.S. If Replimune’s treatment, RP1, worked as well as it did in the clinical trial, Whitman said, as many as 2,500 of those patients could be saved.

RP1 is a genetically engineered virus designed to destroy tumor cells and alert the immune system to swing into action against them. Replimune sought accelerated approval — a sort of shortcut that allows a product to enter the market while a larger confirmatory trial takes place — by presenting data that showed a third of 140 people in the trial had their tumors shrink or disappear. But the agency had warned Replimune in July that it risked denial unless it changed its development plans. In particular, the FDA noted that the trial had no control arm to compare RP1 to an approved melanoma treatment. Instead, all patients were given RP1 along with Opdivo, a type of immunotherapy.

Replimune’s scientists don’t entirely understand how the drug works, but research indicates that, in addition to destroying cancer cells, it releases chemicals that revive Opdivo’s capacity to stimulate the immune system. The company argued it would be unethical to give Opdivo alone as a control arm, because all the patients entered in the trial had already stopped getting better while taking only Opdivo or other drugs in its class.

“Having a control arm would have been unethical,” Wise-Draper said. Some of her patients responded extremely well to RP1 and no longer have evidence of melanoma, she said.

Replimune currently has a larger trial that includes a control arm, but “the bigger question is whether the company will survive,” Whitman said. The FDA-accelerated approval would have persuaded investors to provide enough cash to finish the larger trial, he said.

Replimune did not respond to repeated requests for comment. But [the company told reporters](#) it is firing more than half its staff and closing some operations in the wake of the FDA ruling.

RP1 wouldn't have been the first melanoma drug approved based on a single-arm trial. Keytruda, the best-selling Merck cancer drug, was approved to treat melanoma some 12 years ago based on such a trial design. But in its denial statement, the FDA said it wasn't convinced that the positive effects of the combination regimen were all due to RP1 and not partly to Opdivo.

Replimune arguably could have found an ethical way to set up a control arm for its treatment, Kim said. On the other hand, the FDA could have "given them a provisional yes" with accelerated approval, he said. The whole point of the three-decade-old accelerated approval program is to "take a gamble," Kim said.

The agency's statement, stressing the company's methodology over the result, "is a recalibration of how confident sponsors can be with similar studies," he said.

Vinay Prasad's Final Days at FDA

Much of the criticism of the FDA under Trump has focused on Vinay Prasad, who was fired then rehired last summer and held various leadership roles at the agency. Prasad, an oncologist known for critiquing the statistical bases of studies, repeatedly intervened in approval processes for drugs and vaccines normally decided by lower-ranking FDA professionals.

Prasad, who did not respond to requests for comment, resigned for good May 1, three weeks after the Replimune decision. "There's this lingering question of whether this was Vinay's last stand, or an objective decision made by careful scientists," Kim said.

Makary ran afoul of Trump administration officials over various decisions, the last being his reluctance to approve flavored vapes for smoking cessation. Trump's anti-abortion supporters wanted him ousted for allowing a generic form of mifepristone on the market, and for failing to speed up studies they hoped would lead to the abortion drug's withdrawal from the market.

But in the industries regulated by the FDA, ranging from gene therapy to vaccines and cancer, officials are frustrated by the agency's uncertain direction. In past administrations, the agency generally swung on a narrow arc between loosening and tightening requirements for drug approvals. Under Makary, "it's been swinging in every conceivable direction," Grossman said.

"It's very inconsistent; it's all over the place," Whitman said. "The inconsistency is part of the concern."

During his tenure, Makary made a series of categorical statements that either claim credit for progress made during earlier administrations or exaggerate the agency's ability to move forward on goals.

For example, he set a goal of [ending animal testing](#), which is considered impractical at the moment, Kim said, and moved to [aggressively implement](#) artificial intelligence at the FDA —

prematurely, critics say. Makary and Prasad also promised to reduce the [standard number of required clinical trials](#) from two to one. FDA statutes require two well-controlled clinical trials for drug approvals, but exceptions to that rule are already frequent.

“The FDA is sending signals that it wants to even further reduce the evidence needed to support drug approval,” said Aaron Kesselheim, a Harvard Medical School professor and an expert on the drug industry. “Of course, if we’re talking about vaccines, the total opposite is the case. FDA has been taking real steps to make it harder to get vaccines approved.”

The FDA fired about 4,000 staffers at the start of the Trump administration. Makary promised to hire thousands back, but considering the upheavals at HHS and the FDA, these positions may be hard to fill. “What magic trick will get that done?” Grossman asked.

“The unfortunate thing is that there has been so much chaos at FDA that this Replimune decision, which may have needed to happen, has gotten mired in the controversy,” said Evan Seigerman, leader of healthcare research at BMO Capital Markets.

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