IN DEPTH

President Donald Trump and FDA Commissioner Stephen Hahn (right) met with Gilead CEO Daniel O’Day (left) after remdesivir received an emergency use authorization.

COVID-19

‘A very, very bad look’ for remdesivir

FDA and Europe anointed it as a key therapy just after a major study found it has little value

By Jon Cohen and Kai Kupferschmidt

October was a good month for Gilead, Sciences, the giant U.S. manufacturer of antivirals. On 8 October, the company inked an agreement to supply the European Union with its drug remdesivir as a treatment for COVID-19—a deal potentially worth more than $1 billion. Two weeks later, on 22 October, remdesivir became the first COVID-19 drug approved by the U.S. Food and Drug Administration (FDA). The decisions mean Gilead can cash in big in two major markets, both with soaring COVID-19 cases.

But they baffled scientists who have closely watched the clinical trials of remdesivir unfold over the past 6 months—and who have many questions about its worth. At best, one large, well-designed study found that remdesivir, which must be infused intravenously, modestly reduced the time to recover from COVID-19 in hospitalized patients with severe illness. A few smaller studies found no impact on the disease whatsoever, and none has found that the antiviral reduces patients’ level of SARS-CoV-2, the causative virus. Then, on 15 October, the fourth and largest study delivered what some believed was a coup de grâce: The World Health Organization’s (WHO’s) giant Solidarity trial showed that remdesivir does not reduce mortality or the time COVID-19 patients take to recover.

Science has learned that both FDA’s decision and the EU deal came about under unusual circumstances that gave the company important advantages. FDA never consulted a group of outside experts that it has at the ready to weigh in on complicated antiviral drug issues. FDA can tap that group, the Antimicrobial Drugs Advisory Committee (AMDAC), to review all available data on experimental treatments and then make recommendations about drug approvals—yet it has not convened once during the pandemic.

The EU, meanwhile, agreed to the remdesivir purchase price exactly 1 week before the disappointing Solidarity trial results came out. It was unaware of those results, but Gilead knew the trial was a bust; it had begun to review the data on 23 September. “This is a very, very bad look for the FDA, and the dealings between Gilead and EU make it another layer of badness,” says Eric Topol, a cardiologist at the Scripps Research Translational Institute.

FDA has no obligation to convene the panel for its decisions, stresses AMDAC member David Hardy, an HIV/AIDS scientist of the University of California, Los Angeles. Yet Hardy is “amazed” the agency didn’t consult it in this case. “This sets the standard for the first COVID-19 antiviral,” he says. “That really is something that’s very, very important.”

FDA did not respond to Science’s request to discuss why it opted against convening the committee, noting only that it is “at the discretion” of division directors. But FDA’s inaction stands in sharp contrast to its handling of COVID-19 vaccines; it convened an advisory group to discuss potential dilemmas the very day of the remdesivir approval. Gilead, for its part, acknowledges it had seen an early draft of the Solidarity results before signing the EU deal. But Gilead has aggressively challenged the validity of the data, in part because the study was done in countries with widely varying health care standards.

That criticism has angered Solidarity investigators. Half the patients who received remdesivir were treated in Europe and Canada, WHO notes, and the others were not necessarily in countries with substandard health care. “It’s appalling to see how Gilead tries to badmouth the Solidarity trial,” says Marie-Paule Kieny, director of research at the French medical research agency INSERM and a former WHO officer.

HOPES THAT FADED

On 10 January, 2 days after China revealed SARS-CoV-2 causes COVID-19, researchers published an encouraging study in Nature Communications about remdesivir, originally developed to fight the Ebola and hepatitis C viruses. In both test tube and mouse studies, it had powerful inhibitory effects on a SARS-CoV-2 relative that causes Middle East respiratory syndrome. Two weeks later, doctors treated the first confirmed U.S. case with the drug and reported the 35-year-old man improved rapidly.

An interim analysis from a large-scale clinical trial by the National Institutes of Health (NIH), announced on 29 April, showed the drug reduced the median recovery time of severely ill, hospitalized COVID-19 patients from 15 days to 11 days. A second study, in China, appeared the same day and found no
statistically significant benefit, however. Two days later, FDA granted an emergency use authorization (EUA) that allowed the drug to be given for severe COVID-19, a move President Donald Trump praised in an Oval Office press event with Daniel O’Day, CEO of Gilead.

But the mixed messages about the drug continued: In August, a Gilead-sponsored study showed patients with moderate pneumonia treated for 5 days with remdesivir improved more quickly than those who received standard care, but oddly, those treated for 10 days did not. Nevertheless, shortly afterward, FDA expanded remdesivir’s EUA to include all hospitalized COVID-19 patients.

To Topol, FDA’s move resembled heavily criticized EUAs issued earlier for the malaria drug hydroxychloroquine—which the agency later rescinded—and antibody-rich “convalescent” plasma. In an open letter to FDA Commissioner Stephen Hahn, he wrote: “These repeated breaches demonstrate your willingness to ignore the lack of scientific evidence, and to be complicit with the Trump Administration’s politicization of America’s healthcare institutions.”

Many scientists expected WHO’s Solidarity trial—which had 2750 patients on remdesivir, about three times as many as all other published trials put together—to resolve the drug’s worth. Conducted in 30 countries, Solidarity compared remdesivir and three other repurposed drugs with each other and the standard of care. (Unlike the NIH and Chinese trials, it did not use a placebo.) None of the drugs lowered mortality among hospitalized patients, it found, and the investigators also noted that remdesivir did not affect “the duration of hospitalization” or whether COVID-19 patients required ventilators.

Solidarity described the results to FDA representatives on 10 October and in a preprint posted 5 days later. But 1 week after that, FDA approved the drug, having reviewed data only from the NIH study and two Gilead-sponsored trials. It had ignored the Solidarity data as well as the findings in China.

That infuriated the Solidarity team. “The mantra I’ve always heard as a joke about the FDA is that they say ‘In God we trust, everyone else has to provide data,’” Kieny says. “So look at all the data.”

Gilead Chief Medical Officer Merdad Parsey argued in an open letter posted the day of FDA’s remdesivir approval that Solidarity “does not negate other study results—particularly from a trial designed with the strictest of scientific standards,” like NIH’s study. The company further noted that the Solidarity results have not been peer reviewed and told Science WHO had yet to provide Gilead “the underlying data sets or statistical analysis plan” for the trial.

WHO says Gilead knew the analysis plan before joining the trial and will receive the full data set once the study is complete, and that FDA traditionally reviews all available data, including unpublished findings.

Clifford Lane of the National Institute of Allergy and Infectious Diseases, who helped run the NIH study, says its main difference with Solidarity is “the degree of granularity” of the analyses of subgroups that may have benefited. “I think the Solidarity data are fine,” Lane says. “It’s a very large study and it has a very robust endpoint.”

Richard Peto, a University of Oxford statistician and epidemiologist who helped design Solidarity and analyze the data, stresses that the WHO trial cannot prove remdesivir has no benefit for COVID-19. “Gilead and the FDA have sort of maneuvered us into a position where we’re being asked to try and prove remdesivir does nothing rather than asking the usual way round, which is, ‘Can the manufacturers prove it does something?’”

It’s still possible that remdesivir might help people at early stages of disease, says Martin Landray of Oxford, who is co-leading the world’s largest study of various COVID-19 treatments. But it “definitely doesn’t work in the sickest patients where the biggest gains would be.” Treating patients earlier comes at a price. “You won’t save many lives, and you’ll have to treat a lot of patients,” he says. “And it’ll cost you a fortune.”

At the same time, the trials have not ruled out the possibility of harmful side effects. In late August, WHO noted a disproportionately high number of reports of liver and kidney problems in patients on remdesivir. And the European Medicines Agency (EMA) said last month that its safety committee had begun to assess reports of acute kidney injuries in some patients taking the drug.

To many scientists, such complexities underscored that FDA should have consulted AMDAC, its panel of outside experts, for a vigorous debate. It could have “elevated the discussion,” says AMDAC Chair Lindsey Baden, an infectious disease specialist at Brigham and Women’s Hospital. “Hydroxychloroquine, convalescent plasma, remdesivir—these are the only information blacked out was results relating to the other drugs used in the trial because of confidentiality agreements.

Although the agreement with Gilead locks EU members into a price of about $2400 for a full course of remdesivir, it does not obligate any countries to purchase the drug, the Commission spokesperson says. But Yannis Natsis of the nonprofit European Public Health Alliance says that given the Solidarity results, the European Union “should at least renegotiate the volume of the doses and the price.”

To Kieny, this investment in a drug that may help just a few patients is an “enormous” waste. “You can always say, ‘OK, now, if I disaggregate the population and if I take only those who have a blue eye and a wooden leg, maybe this is very effective,’” she says.

On 28 October, Gilead told investors that remdesivir has brought in $873 million so far this year. “We’re proud to be at the front end of this with a very potent antiviral,” O’Day said. ■
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