Policy Implications of the Orphan Drug Designation for Remdesivir to Treat COVID-19

On March 23, 2020, the US Food and Drug Administration (FDA) granted Gilead Science an orphan drug designation for remdesivir to treat coronavirus disease 2019 (COVID-19), even though this status is usually reserved for drugs that treat rare diseases. In explaining its decision, the agency stated that at the time of Gilead’s application for designation, there were sufficiently few confirmed cases of COVID-19 in the United States that remdesivir met criteria for designation under the Orphan Drug Act of 1983.

The FDA’s decision sparked immediate criticism. A group of 51 advocacy organizations wrote a letter to the chief executive officer of Gilead calling the designation an “unconscionable abuse” of orphan drug policy. Perhaps due to the intense public backlash, Gilead asked the FDA to revoke the orphan drug designation just 2 days after it was granted.

In our view, the orphan drug designation for remdesivir was inconsistent with the purpose of the Orphan Drug Act. This designation also highlights a loophole in orphan drug policy that could be used again.

The Orphan Drug Act
The Orphan Drug Act of 1983 provides incentives for the development of drugs to treat rare diseases. Sponsors can receive these incentives if a drug meets 1 of the 2 criteria for orphan drug designation. Typically, as was the case for remdesivir, the FDA grants a designation because the drug would treat a disease affecting fewer than 200,000 people in the US. In unusual circumstances, the agency grants a designation for drugs that would treat a common disease after the sponsor demonstrates that the likely sales would be insufficient to recoup development and marketing costs.

Once a designation is granted, sponsors receive a 25% federal tax credit for the costs of clinical testing and are also eligible to apply for FDA grants to further defray these costs. If an orphan-designated drug receives FDA approval for an orphan indication, the Orphan Drug Act provides sponsors with a 7-year period of “orphan drug exclusivity” during which competitors are barred from marketing the same drug to treat the same disease.

The purpose of these incentives is to promote the development of drugs for rare diseases that otherwise may not be brought to market because of their limited sales potential. COVID-19, however, is not a rare disease in the US. As of April 3, 2020—just 11 days after the FDA granted remdesivir the designation—the number of confirmed US cases of COVID-19 surpassed 200,000.

Clearly, the orphan drug designation for remdesivir was inconsistent with the purpose of the Orphan Drug Act.

Remdesivir and the Orphan Drug Act
Although it can be argued that the FDA could have chosen not to grant orphan drug designation for remdesivir to treat COVID-19, our view is that the agency had little ability to deny Gilead’s application. Under the Orphan Drug Act, FDA must evaluate applications for designation based on information at the time of application. Gi-lead has stated that it sought designation in early March 2020. As of March 15, 2020, there were 2918 confirmed US cases of COVID-19, so COVID-19 was a “rare” disease at the time of application.

The FDA also would have had little ability to revoke the orphan drug designation for remdesivir had Gilead not asked the agency to do so. The FDA regulations would have prevented the agency from revoking the designation solely because the prevalence of COVID-19 grew beyond 200,000 cases. The FDA could have revoked the designation if it had concluded that remdesivir had not been eligible for designation at the time of application; for example if the agency later determined that the prevalence of COVID-19 exceeded 200,000 cases in early March 2020 due to widespread undertesting. However, given the small number of confirmed cases and limited testing capacity in early March, such a retrospective determination would have been difficult to justify.

Federal Legislation to Close the Loophole
The FDA’s limited ability to deny orphan drug designation for a drug that treats a rapidly spreading disease, coupled with its limited ability to revoke this designation once the disease is no longer rare, creates a loophole that drug sponsors could use again. To close this loophole, Congress could amend the Orphan Drug Act so that the FDA can revoke an orphan drug designation granted based on disease prevalence if the number of affected people in the US later exceeds 200,000. Alternatively, Congress could limit or terminate orphan drug exclusivity once the product was deemed sufficiently profitable, following the approach of a policy in the European Union.

For sponsors considering applying for an orphan drug designation to treat a disease that may soon become widespread, the prospect of a short-lived designation or exclusivity period might decrease the motivation to apply.

Implications for Orphan Drug Policy
The orphan drug designation for remdesivir adds to prior concerns about the exploitation of loopholes in the Orphan Drug Act. For example, adalimumab (Humira; AbbVie), a tumor necrosis factor blocking agent, was the top-selling prescription drug in the US with $13.7 billion in sales in 2018. Despite these block-
bustor sales and the fact that adalimumab is most often used for non-rare diseases such as rheumatoid arthritis, psoriasis, Crohn disease, and ulcerative colitis. AbbVie has obtained 7 orphan indications from the FDA, each of which entitled the sponsor to orphan drug benefits. Of the 7 orphan indications, 6 are for different age-based subpopulations of patients with juvenile idiopathic arthritis, uveitis, or hidradenitis suppurativa. Of the basis of this and other examples, drug sponsors have been criticized for pursuing a strategy of partitioning diseases by patient age or disease subtype to create populations that are artificially rare.

A second example is extended-release buprenorphine injection (Sublocade; Indivior). In 2017, the FDA approved this drug to treat opioid use disorder under a 1994 orphan drug designation for buprenorphine sublingual tablets (Subutex) granted to Indivior’s parent company, Reckitt-Benckiser. The 2017 approval for Sublocade potentially would have entitled Indivior to a 7-year period of orphan drug exclusivity during which other buprenorphine products could not have been marketed. The FDA granted the designation based on Reckitt-Benckiser’s argument that sales would be insufficient to recoup development costs, and extended this designation to Sublocade even though Subutex had $285 million in sales between 2002 and 2011. In 2019, however, the FDA revoked the designation for Subutex after concluding that Reckitt-Benckiser’s 1994 cost-recovery analysis was based on unreasonable assumptions. For example, the analysis assumed that Subutex would only be in prescribed in methadone outpatient treatment programs—the only settings in which buprenorphine could be prescribed in 1994—even though it was likely at the time that restrictions on buprenorphine prescribing would be loosened owing to the drug’s safety, allowing it to be used in additional settings.

Conclusions

The examples of remdesivir and Sublocade illustrate how drug sponsors have taken advantage of policy loopholes to obtain orphan drug benefits for drugs that address public health crises, such as the opioid epidemic and the COVID-19 pandemic. Opioid use disorder and COVID-19 are not rare diseases. Congress and the FDA should ensure that the benefits of the Orphan Drug Act are only used in a manner consistent with their purpose.