VIEWPOINT

Missed Opportunities on Emergency Remdesivir Use

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On May 1, the US Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for remdesivir for the treatment of hospitalized adults and children with severe coronavirus disease 2019 (COVID-19). An EUA permits the use of an unapproved drug, biologic, or medical device and may be issued by the FDA when the secretary of Health and Human Services has declared a public health emergency "that has a significant potential to affect national security or the health and security of United States citizens living abroad."[1] As seen with the FDA's recent revocation of the EUA for hydroxychloroquine, the agency has wide discretion to revoke or revise EUAs when appropriate for public health (the FDA does not have comparable authority to act so quickly with respect to drugs that have been approved).

In the case of remdesivir, the decision to grant an EUA followed the release of a summary interim finding of shorter time to recovery among patients treated with the drug in a National Institute of Allergy and Infectious Diseases (NIAID)–funded phase 3 placebo-controlled clinical trial. In the immediate wake of the EUA, attention focused on the equitable distribution of the limited supply of remdesivir.[2] However, 2 deeper concerns exist.

First, the EUA does not ensure continued robust evidence generation despite outstanding questions over the safety and efficacy of the drug. Subsequently published results of the NIAID trial based on 1059 patients showed a median 4-day shorter recovery time associated with remdesivir, but did not show a significant increase in survival among patients receiving it.[3] A separate phase 3 placebo-controlled trial in China involving 237 patients did not find significant clinical benefits from use of remdesivir in a similar patient population (but was reportedly stopped early because of inadequate enrollment),[4] and currently unpublished results of another phase 3 trial reportedly did not identify significant clinical improvement among 393 hospitalized patients with moderate COVID-19 who received 10 days of treatment vs standard of care.[5]

Nevertheless, in light of the interim analysis of the NIAID-funded trial, remdesivir can now be offered to patients who had been receiving placebo in the trial, increasing the importance of assessments of the drug in clinical settings to answer unresolved therapeutic questions. Even though the FDA has broad power to impose "appropriate conditions with respect to the collection and analysis of information concerning the safety and effectiveness" of remdesivir,[1] the EUA does not contain terms adequate for monitoring the drug's use or outcomes. Instead, under the EUA, physicians seeking to administer remdesivir must be given a 36-page fact sheet highlighting instructions for use, possible risks, and required reporting of suspected medication-related serious adverse events through the FDA's passive surveillance system, which has historically been limited by underreporting and incomplete reporting.

Second, the pricing of remdesivir has not yet been set. Gilead, the manufacturer of remdesivir, has offered to donate 940 000 doses of the drug to the federal government, enough to treat approximately 85 000 to 157 000 patients. However, the manufacturer has stated that it will soon start charging for the drug, which analysts estimate will be used to treat thousands more individuals in the US and may be heavily stockpiled by the federal government. In May, the Institute for Clinical and Economic Review (ICER), an independent nonprofit group that performs cost-effective analyses for drugs, estimated that based on preliminary data and an assumption of a mortality benefit yet to be demonstrated, a cost-effective price for a 10-day course of remdesivir would be approximately $4500.[6] ICER also cited data suggesting that a minimal price to recover the costs of drug production could be as low as $10, not including future spending on research and development specific to COVID-19, on the grounds that earlier research and development costs had already been recouped from Gilead's successful marketing of drugs for hepatitis C virus, for which remdesivir was originally developed. Gilead has yet to comment on these estimates for what the bounds of a reasonable price could be.

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It is not too late to address either shortcoming. First, the FDA should revise its current EUA for remdesivir to require the creation of a patient registry that includes information on patient demographics, treatment dose and duration, and safety outcomes. Physicians who prescribe the drug would be responsible for reporting this information to the registry. Such registries are routinely required as part of risk evaluation and mitigation strategy (REMS) programs that the FDA imposes on drugs with special risks and can help in the identification of important safety signals. To avoid past missteps that occurred with REMS programs,[7] the registry should be run by the FDA or an independent third party (as opposed to the manufacturer) with deidentified data made publicly available. This recommendation is consistent with the suggestion by White and Angus[8] that much

more could be learned from the "natural experiment" of the distribution of remdesivir via a state-level "lottery" and what will likely be other drugs in limited supply.

Such a registry would have the added benefit of enabling monitoring of disparities in access. COVID-19 has disproportionally affected racial and ethnic minorities in the US. In an analysis of a representative sample of 580 hospitalized patients with COVID-19 with available race or ethnicity data across 99 counties in 14 states, the Centers for Disease Control and Prevention reported that black and Hispanic individuals made up 41% of patients but only 32% of the catchment area populations.[9] Historically, racial and ethnic minority populations have been slower to receive innovative treatments, an outcome that could be prevented or, at minimum, identified and remedied through transparent reporting.

The federal government should also commence negotiations with Gilead over an appropriate price for the drug. Remdesivir will not solve the pandemic, but it does appear to have some efficacy in reducing recovery time. This should be reflected in its price, which will serve as a signal to other innovators that their efforts will be fairly rewarded.

However, in the case of remdesivir, the price should also reflect the outsized role the US government had in its development. The phase 3 NIAID-designed and government-funded trial is only the most recent example of federal investment in the drug.[10] In 2014, Gilead entered into a research contract with the US Army Medical Research Institute for Infectious Disease to scan Gilead's library of molecules for potential treatments for Ebola virus disease. Among the candidates identified was remdesivir. Gilead conducted a phase 1 trial to evaluate the safety of the drug in humans, but more advanced studies, including investigations of the effectiveness of remdesivir against Ebola, were designed and funded by NIAID. Through these contributions, taxpayers assumed greater risk as clinical development progressed. This arrangement departs from the typical model of risk sharing, in which pharmaceutical manufacturers assume the primary costs of late-stage drug development, with the lure of market exclusivity and, thus, the ability to price what the market will bear. The trade-off for this off-loading of risk should be affordable access to the product. Such accounting would importantly still permit Gilead to profit from creating value but would be commensurate with its risk-taking.

Ultimately, the EUA for remdesivir presents a critical opportunity for the federal government to set a precedent for future emergency use authorization of investigational drugs in the COVID-19 pandemic and beyond. A framework to ensure adequate safety monitoring and reasonable pricing based on risk-taking, efficacy, and safety would be a positive legacy.

ARTICLE INFORMATION

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REFERENCES

1. Federal Food, Drug, and Cosmetic Act, §360bbb-3: Authorization for medical products for use in emergencies, 21 USC §360bbb-3 (2011).

2. Ison MG, Wolfe C, Boucher HW. Emergency use authorization of remdesivir: the need for a transparent distribution process. *JAMA*. 2020;323(23):2365-2366. doi:10.1001/jama.2020.8863

3. Beigel JH, Tomashek KM, Dodd LE, et al; ACTT-1 Study Group Members. Remdesivir for the treatment of Covid-19—preliminary report. *N Engl J Med*. Published online May 22, 2020. doi:10.1056/NEJMoa2007764

4. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet*. 2020;395(10236):1569-1578. doi:10.1016/S0140-6736(20)31022-9

5. Langreth R. Gilead falls as drug has only small benefit in large trial. *Bloomberg News*. Updated June 1, 2020. Accessed June 18, 2020. https://www.bloomberg.com/news/articles/2020-06-01/gilead-drug-has-only-modest-benefit-in-large-trial-shares-fall

6. Institute for Clinical and Economic Review. Alternative pricing models for remdesivir and other potential treatment for COVID-19. Updated May 1, 2020. Accessed June 18, 2020. https://icer-review.org/wp-content/uploads/2020/05/ICER-COVID_Initial_Abstract_05012020-3.pdf

7. Sarpatwari A, Curfman G. Mitigating health risks of prescription drugs: lessons from FDA oversight of opioid products. *JAMA*. 2019;321(7):651-653. doi:10.1001/jama.2019.0236

8. White DB, Angus DC. A proposed lottery system to allocate scarce COVID-19 medications: promoting fairness and generating knowledge. *JAMA*. Published online June 24, 2020. doi:10.1001/jama.2020.11464

9. Garg S, Kim L, Whitaker M, et al. Hospitalization rates and characteristics of patients hospitalized with laboratory-confirmed coronavirus disease 2019—COVID-NET, 14 States, March 1-30, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(15):458-464. doi:10.15585/mmwr.mm6915e3

10. Eastman RT, Roth JS, Brimacombe KR, et al. Remdesivir: a review of its discovery and development leading to Emergency Use Authorization for treatment of COVID-19. *ACS Cent Sci*. 2020;6(5):672-683. doi:10.1021/acscentsci.0c00489