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Building Bridges and Providing Transparency to the Hepatitis C Virus Drug Approval Process

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Chronic hepatitis C is a major cause of cirrhosis and hepato-cellular carcinoma worldwide¹ and the leading indication for adult liver transplants in the United States and Europe.² Although the incidence of chronic hepatitis C is declining in the developed world, the number of deaths owing to complications of the infection is estimated to increase over the next decade.³ A parallel rise in the cost of managing complications of advanced chronic hepatitis C is projected to increase from a current \$6.5 billion to approximately \$9.1 billion in 2024 in the United States.⁴ Modeling data suggest that implementation of a national screening program linked to effective therapy would have a substantial impact on reducing the burden of disease resulting from chronic hepatitis C.⁵ The development of highly effective, safe therapies for chronic hepatitis C holds promise to improve the outcomes of patients with chronic hepatitis C.⁶

In December 2013, a potentially game-changing drug, sofosbuvir, a hepatitis C virus NS5B polymerase nucleotide analog inhibitor, was approved by the US Food and Drug Administration (FDA). This drug was afforded breakthrough status (defined as a drug that treats a serious or life-threatening condition and for which preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies) by the FDA, which allowed it to receive an expedited review.⁷

In seeking approval, the sponsor submitted evidence from 13 phase I, 6 phase II, and 5 phase III trials to support licensing of sofosbuvir in combination with other agents in adults with HCV genotypes 1–6. Notably, only a single-arm, uncontrolled trial was provided as evidence of the drug's safety and efficacy among untreated patients with HCV genotype 1 in combination with peginterferon alpha and ribavirin.⁸ For drug approval, the FDA generally requires 2 studies to show clear evidence of drug effectiveness. In addition, concerns were raised during the review process about the lack of evidence supporting the indication for sofosbuvir with peginterferon and ribavirin in HCV genotype 1 treatment-experienced patients. Ultimately, sofosbuvir was granted approval for both untreated and previously treated populations.

In this issue of *Gastroenterology*, the FDA provides a commentary with a detailed summary of the rationale supporting their recommendation to approve the use of sofosbuvir in

Conflicts of interest

The authors disclose no conflicts.

combination with peginterferon and ribavirin in a population that previously failed therapy in the absence of clinical data.⁹ The FDA cited 3 pieces of evidence that supported the use of sofosbuvir in treatment-experienced patients. First, the FDA reasoned that the high sustained virologic response (SVR) rate (89%) achieved by treatment-naïve HCV genotype 1 subjects enrolled in the NEUTRINO trial suggested that the regimen would be effective in nonresponders because peginterferon and ribavirin are associated with a failure rate of approximately 50% in untreated HCV genotype 1 patients. Second, having verified that a combination of pretreatment host and viral factors (interleukin [IL]-28B non-CC genotype, high viral load [$>800,000$ IU/mL] and presence of F3/F4 fibrosis) derived from analyses of previously published studies could be used to identify untreated patients who would likely fail a peginterferon and ribavirin regimen, it was hypothesized that patients with these baseline characteristics enrolled in NEUTRINO would be representative of the SVR rate of nonresponders to peginterferon and ribavirin. The SVR rate among patients with these pretreatment characteristics (presumed nonresponders) in the NEUTRINO trial was shown to be substantially higher, 71% compared with the observed rate of 5% and 20% in null and partial responders, respectively, retreated with peginterferon and ribavirin. Third, the SVR rates were extrapolated for prior null responders to peginterferon and ribavirin based on an assumption of equivalent odds ratios and relative risk between sofosbuvir plus peginterferon and ribavirin and previous HCV regimens. Taken together, these analyses, which “bridge” data from varying sources, provided evidence that sofosbuvir in combination with peginterferon and ribavirin would have, at a minimum, similar effectiveness as other approved regimens.

Although persuasive, this method raises several issues. Should modeling data be used to inform the approval process and how confident can clinicians be of treating patients with a regimen that has not been formally tested in the intended population? With regard to the first question, the FDA’s perspective on this can be summarized briefly: “Bridging knowledge to provide clinical evidence of effectiveness and to support dosing recommendations not only is acceptable from a regulatory perspective, but when scientifically supported and warranted is also encouraged to increase the efficiency by which new drugs and optimal dosing recommendations are made available to patients in need.”¹⁰ There is also a precedent for this with other drugs such as oxcarbazepine and topiramate being approved for the treatment of partial seizures in a pediatric population without a controlled clinical trial and levofloxacin for the treatment of postexposure inhalation anthrax.^{11,12} Indeed, between 2000 and 2008, pharmacometric analyses influenced drug approval and labeling decisions for $>60\%$ of submissions to the FDA.¹² For the second question, clinicians can take assurance that response rate predictions generated from bridging analyses with boceprevir and telaprevir in untested populations closely approximated the eventual clinical data. For example, in the boceprevir trial of treatment-experienced patients, patients who failed to achieve a >2 -log reduction in HCV RNA by week 12 (null responders) were specifically excluded. Modeling data predicted an SVR rate of 31%–38% in null responders treated with boceprevir.¹³ Results from PROVIDE, a retreatment trial of persons who failed to achieve an SVR with peginterferon and ribavirin in the control arms of the phase II and III trials of boceprevir revealed an SVR rate of 38% among null responders.¹⁴ Similarly, with telaprevir, response-guided therapy (ie, shortening the duration of therapy in patients who achieve early virologic

clearance) was never evaluated prospectively for relapsers, but was approved provided patients achieved undetectable HCV RNA from weeks 4 through 12 (extended rapid virologic response).¹⁵ Response rates generated from the post-approval data in clinical practice demonstrated that the SVR rates approximated the modeling data in relapser patients.^{16,17} These examples suggest that the modeling data are robust. Moreover, with regard to approval of sofosbuvir, the FDA were also influenced by its good safety profile, simple regimen, and short duration of treatment compared with the highly complex regimens with serious side effects that were available for HCV genotype 1 patients.

One other point is worth mentioning. The FDA was able to conduct these bridging analyses in part owing to the large number of databases in their possession provided by sponsors of clinical trials as part of the approval process of other antiviral agents. These datasets contain a wealth of information that could be used to address important supplementary questions regarding treatment.

The FDA is charged by the Food and Drug and Cosmetics Act to approve drugs based on substantial evidence of safety and effectiveness. To improve and expedite the approval process, the FDA often applies alternate sources of evidence. However, the process has to be totally transparent and justified with compelling rationale. If a pharmaco-metric approach will be used in the approval process, at a minimum, phase II data should exist and there should be a requirement for follow-up studies to be performed. In addition, extensive postapproval monitoring is necessary to address the drug toxicity issue more fully. As the FDA continues to assess a full pipeline of anti-HCV drugs, it should apply a similar process to expedite other potentially effective and safe treatment regimens, especially in light of the exorbitant cost of the current drugs. However, once safe and efficient therapies are available for hepatitis C, regulators should be less reliant on modeling data and ensure that appropriate clinical studies are conducted to inform the labeling process. With the ultimate goal of improving treatment outcomes for patients with chronic hepatitis C, it is hoped that the FDA, academic investigators, and industry will work collaboratively and bridge their efforts to thoroughly harness the potential of the vast amount of data generated from many large clinical trials.

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