

FDA Review Vouchers

TO THE EDITOR: In his Perspective article, Kesselheim (Nov. 6 issue)¹ expresses concern about priority-review vouchers for drugs for the treatment of neglected tropical diseases. We proposed the voucher program in 2006,² it became law in 2007, and the law allows vouchers to be awarded by the Food and Drug Administration (FDA) in 2009.² Under the law, developers of treatments for neglected diseases such as malaria and tuberculosis are rewarded with priority-review vouchers to be applied to other drugs, such as profitable cardiovascular therapies. Kesselheim says that this prize system is “potentially dangerous” and “inefficient,” and he suggests that it is ineffective and too narrow in scope.

First, priority review is safe.³ Priority review should not be confused with “accelerated approval” or “fast track.” Priority review does not omit safety or efficacy studies or require approval within a given time frame. It sets a target of 6 rather than 10 months for FDA review.

Second, the voucher program is efficient because it can alleviate tremendous suffering at little government cost. Our analysis shows that it will provide substantial net benefits to patients and drug developers,² while the additional cost of priority review will be covered by an extra user fee paid to the FDA.

Third, the voucher program will be effective. Kesselheim argues that “manufacturers will be unlikely to start such a program merely because of the prospect of earning a voucher some years in the future, since the voucher’s value depends on the success of potential ‘blockbuster’ drugs.” Uncertainty is in the nature of the pharmaceutical business. The voucher could be worth more than \$100 million, which should at least motivate firms to take products off their shelves and put them into late-stage clinical trials.

Fourth, the voucher program is of reasonable scope. Kesselheim argues that the scope is too narrow because the voucher prize is not given to manufacturers of follow-on formulations. Conversely, some argue that the scope is too broad, in that vouchers are awarded to manufacturers of treatments that are already available in countries outside the United States. We respect suggestions for improving the law’s provisions, but we think the current compromise is reasonable. The current

priority-review voucher program can provide new incentives for drug development at relatively low government cost, speed the review of another product that the market values, and even speed approval of the generic version of that product.

Other mechanisms are also worthwhile, and we hope that the priority-review voucher program will complement them. Selling a voucher can provide funds for private development partnerships. We also support funds for push mechanisms (e.g., funding of clinical trials) and pull mechanisms (e.g., advance market commitments).⁴

Jeffrey Moe, Ph.D.

Henry Grabowski, Ph.D.

David Ridley, Ph.D.

Duke University
Durham, NC 27708
david.ridley@duke.edu

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THE AUTHOR REPLIES: In response to Moe et al.: there are well-documented concerns about the safety and cost-effectiveness of a priority-review voucher program. A recent study showed that drugs that are approved by the FDA in the last 2 months before a regulatory deadline are more likely to be associated with safety problems than drugs approved at other times, suggesting that there are dangers in imposing arbitrarily accelerated deadlines on FDA reviews.¹ Second, the cost of a priority-review voucher will be substantial because the public will pay more for the earlier availability of drugs such as ezetimibe (Zetia) that may not work better than less-expensive generic drugs.²

Finally, with regard to the treatment of neglected diseases affecting millions of patients

across the world, Moe et al. argue that many promising drugs that are ready for late-stage development have not been taken off manufacturers' shelves because of insufficient financial incentives. If true, this is an alarming indictment of the industry. Pharmaceutical development is largely driven by companies that derive their revenues from patent-protected market exclusivity. In addition to inadequately addressing "unprofitable" diseases, this incentive structure has been exploited by manufacturers to garner undeserved revenue at the expense of patients and payers.³

It is not a stretch to predict similar behavior after the adoption of a priority-review voucher program. The first voucher is likely to be received by Novartis for the antimalarial treatment artemether-lumefantrine (Coartem), a product that has long been available outside the United States.⁴ Yet there is no guarantee that Novartis's windfall of \$100 million (or more) in this case will be invested in delivery of the drug to needy patients or in further research.⁵ The optimal way

to address neglected diseases is not to create ever more convoluted incentives that are easily prone to misuse, but instead to enhance public investment in research while ensuring that the results are made available in such a way as to achieve the greatest benefit for the public health.

Aaron S. Kesselheim, M.D., J.D.

Brigham and Women's Hospital
Boston, MA 02115

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Bezafibrate for an Inborn Mitochondrial Beta-Oxidation Defect

TO THE EDITOR: Carnitine palmitoyltransferase II (CPT2) deficiency is a rare autosomal recessive disorder of mitochondrial fatty acid oxidation. The most common form of this disorder is characterized by muscle stiffness, myalgia, and exercise intolerance,^{1,2} and current dietary approaches often do not prevent attacks of rhabdomyolysis. We found that bezafibrate, a commonly used hypolipidemic drug,³ restored the capacity for normal fatty acid oxidation in muscle cells from patients with a mild form of CPT2 deficiency by stimulating the expression of the mutated gene.⁴

We evaluated the efficacy of bezafibrate as a treatment for the mild form of CPT2 deficiency in six adults; bezafibrate was administered for 6 months (at a dose of three 200-mg tablets per day). The primary end point was the level of fatty acid oxidation in skeletal muscle. Muscle-biopsy specimens were obtained before and after treatment, mitochondria were isolated, and mitochondrial respiration rates were measured in the presence of palmitoyl L-carnitine, the specific substrate of CPT2. Before treatment, the palmitoyl L-carnitine oxidation levels were markedly re-

duced (by 21 to 54% of the normal value), reductions that were consistent with CPT2 deficiency. After bezafibrate treatment, the values increased significantly in the six patients (by 60 to 284%, $P=0.03$) (Fig. 1A). In addition, CPT2 messenger RNA in skeletal muscle increased in all the patients (by 20 to 93%, $P=0.002$) (Fig. 1B), as did the CPT2 protein level (data not shown), findings that were consistent with the increased oxidation levels. In vitro analysis of myoblasts from the patients (Fig. 1C) showed that the initial defect in fatty acid oxidation (49 to 75% of control values) was fully corrected after the cells had been exposed to bezafibrate ($P=0.002$). There were 3 to 24 episodes of rhabdomyolysis per patient over a 6-month period before treatment (mean [±SD] creatine kinase level, $10,900\pm 3900$ IU per liter) and 0 to 6 episodes per patient during treatment (mean creatine kinase level, 4700 ± 1900 IU per liter).

The effects of bezafibrate on health, physical functioning, and quality of life were evaluated with the use of the 36-Item Short-Form General Health Survey, which was completed by each patient before and after treatment. The scores for