

EDITORIALS



Safer Drugs for the American People

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By wide margins, both the House and the Senate have now passed bills that aim to ensure the safety of the drug supply in the United States.^{1,2} Given the serious safety problems that have arisen with drugs taken by millions of Americans, this legislation is long overdue. It is now up to both houses of Congress to resolve the differences between the two versions and agree on a strong final bill to send to the President.

This year, Congress had to consider reauthorization of the Prescription Drug User Fee Act (PDUFA), which it must do every 5 years. Under PDUFA, the major funding for the review of new drugs by the Food and Drug Administration (FDA) comes from user fees paid by pharmaceutical companies. This mechanism has been controversial because, although it was designed to accelerate the drug-approval process and can make new drugs available to patients without delay, it has directed no money to the postmarketing assessment of drug safety. In addition, some believe that user fees pose a conflict of interest for the FDA. Nonetheless, to ensure that the FDA has adequate financial resources, both the House and the Senate versions of the bill not only maintain these user fees but increase them (with some of the money now directed to safety assessment).

In reauthorizing PDUFA, Congress has wisely taken the opportunity to strengthen the FDA's authority over drug safety, and both versions of the bill give the FDA new tools to accomplish this objective. At a minimum, we believe that the final bill should contain the following essential components.

The FDA must have the authority to mandate adequately powered postmarketing clinical trials of the safety of approved drugs and to require specific timetables for their completion and reporting of results.

The FDA must also have the authority to conduct an annual review of drug safety for the first 3 years after a drug's approval and again at 7 years.

To assist patients in reporting adverse effects of the drugs they are taking, drug advertisements and labels must include a toll-free telephone number and a Web address.

There must be substantial penalties for drug advertising that overstates efficacy or understates adverse effects.

The FDA must be able to mandate changes to drug labels as new information about safety and efficacy becomes available.

In order to provide safety surveillance, every new drug should have a pharmacovigilance plan at the time of its approval. Sophisticated pharmacoepidemiologic surveillance systems must be created to allow the FDA to monitor reports of adverse drug effects in large databases.

Clinical trials of drugs must be registered in a public database.

In the wake of the landmark report on drug safety issued by the Institute of Medicine almost a year ago,³ Congress is now poised to pass the most important drug-safety legislation in a century. Although we remain concerned about the user-fee approach to funding of the FDA, we believe that the bills initiated by Congressmen Henry Waxman and Edward Markey and by Senators Edward Kennedy and Michael Enzi are important steps in the right direction. Congress should now speedily agree on a substantive drug-safety bill and give the FDA the tools it needs to do its work. The crisis of confidence in the nation's drug supply must be resolved.

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1. H.R. 2900, 110th Cong. (2007).

2. S. 1082, 110th Cong., 1st Sess. (2007).
 3. Committee on the Assessment of the US Drug Safety System, Baciu A, Stratton K, Burke SP, eds. *The future of drug safety: promoting and protecting the health of the public*. Washington,

DC: National Academies Press, 2006. (Available at <http://www.iom.edu/CMS/3793/26341/37329.aspx>.)

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Prophylactic Treatment for Prevention of Joint Disease in Hemophilia — Cost versus Benefit

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Patients with severe hemophilia number only around 400,000 worldwide, but their lifespan has increased because of improved treatment, and with that the prevalence of the disease is increasing. Despite the relatively small number of patients with severe hemophilia, the disease has an important socioeconomic effect because of its distinctive feature: a level of clotting factor (factor VIII or factor IX) so low that without replacement therapy, frequent hemorrhages occur, most often in the ankle, knee, and elbow joints. These joint hemorrhages culminate in a severe arthropathy, with signs of inflammation (as in rheumatoid arthritis) as well as degenerative damage (as in osteoarthritis).^{1,2} As a result of these hemorrhages, patients with hemophilic arthropathy can become disabled at a relatively young age.

Joint bleeding in hemophilia can be prevented by the administration of a concentrated clotting factor derived from plasma (cryoprecipitate) or a recombinant clotting protein. Since these products are expensive, the beneficial results they have to offer should be balanced by a consideration of their cost.

In this issue of the *Journal*, Manco-Johnson and colleagues report the results of a randomized study that assessed the clinical benefit of a very costly product, recombinant factor VIII, for the prophylactic treatment of young boys (up to the age of 6 years) with severe hemophilia.³ Prophylaxis, a scheduled intravenous injection of clotting factor in anticipation of bleeding, was compared with on-demand, or episodic, treatment, the administration of clotting factor whenever signs of joint bleeding appeared. The benefit of prophylaxis as compared with episodic treatment was clear. After a mean follow-up of 49 months, 93% of the patients in the prophylaxis group showed no joint damage on magnetic resonance imaging as compared with 55% in the episodic-

therapy group. The number of infused units of factor VIII per participant was approximately 350,000 in the prophylaxis group (with 0.63 joint hemorrhage per year) and approximately 113,000 in the episodic-therapy group (with 4.89 joint hemorrhages per year). Several previous retrospective or uncontrolled studies have suggested the superiority of prophylaxis,^{4,5} but the study by Manco-Johnson et al. is a controlled randomized trial comparing the effects of prophylaxis with episodic treatment in hemophilia.

The study puts a harsh light on cost-benefit issues in the management of hemophilia: the estimated annual cost for prophylactic treatment of one patient with recombinant factor VIII was \$300,000. Manco-Johnson and her colleagues comment that “the high cost of recombinant factor VIII is a barrier to widespread acceptance of prophylaxis.” With the current challenges entailed in reducing health care costs, this is a reality we must deal with, a challenge to further optimize the balance between cost and benefit.

In the balance of cost with the efficacy of treatment in hemophilia, it is important to consider that inadequately treated patients make great demands on the health care system. Such patients often need expensive additional treatment, such as joint replacement. Yet the kind of cost-effectiveness studies that have been performed for many other chronic diseases have never been performed for hemophilia. The dilemma in managing hemophilia is not whether to use prophylaxis or episodic treatment but how to manage prophylaxis such that the optimal, most cost-effective treatment is provided.

The crux of the problem is this: How many joint hemorrhages can be tolerated before disabling arthropathy occurs, and how can clotting-factor replacement therapy be managed such that optimal prevention of joint bleeding is achieved?