

CORRESPONDENCE



A New Approach to Drug Development

TO THE EDITOR: In his Sounding Board article calling for changes in the drug-approval process, Wood (Aug. 10 issue)¹ does not consider a very important concept. What if basic research points toward a simpler and cheaper way to treat, control, or cure one of the chronic disorders? The history of the discovery of niacin as a cure for pellagra is a prime example of such an effort. We cannot expect pharmaceutical companies to take on such tasks.

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1. Wood AJJ. A proposal for radical changes in the drug-approval process. *N Engl J Med* 2006;355:618-23.

TO THE EDITOR: Although Wood's ideas for changing the drug-approval process are interesting, physicians should be taught and encouraged to use evidence-based medical skills and critical thinking to evaluate the effectiveness of new drugs and should be rewarded for doing so. Such a move would reduce the influence of pharmaceutical companies and lead to changes in prescribing practices that would accomplish the same goals that Dr. Wood would like to see accomplished through government regulation and market reforms. The prohibition of direct-to-consumer advertising and other drug-company spending to influence (allegedly, to educate) physicians might help more than any other change to improve the way that new drugs are used.

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TO THE EDITOR: I was pleased to see a thoughtful proposal addressing ongoing difficulties with the

development of socially useful drugs. However, I was somewhat surprised that in a proposal from a physician who could benefit substantially from his plan (through capital investments mentioned in the disclosure statement), there is no mention of the cost to society of extending exclusivity protection to pharmaceutical companies. Wood's proposal would diffuse the increased cost of drug development, but it is not clear whether such a system would be cheaper overall than, for instance, a system in which the government directly subsidized the development of needed drugs or dramatically reduced the exclusivity of drugs with minimal social benefit.

In Wood's plan, the profits used to entice pharmaceutical companies to pursue the responsible development of drugs would come from the government, insurance companies, and patients themselves and would have the potential to substantially exceed the marginal cost of developing important drugs. Wood's ideas merit discussion, but we must not pretend that his proposal would not involve substantial costs in terms of prolonged high prices for new drugs.

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TO THE EDITOR: As Wood notes, the majority of drugs now being sold were developed through funding from the National Institutes of Health. Thus, taxpayers have already paid for the discovery of such drugs. Furthermore, virtually all of industry's decisions regarding drug development are based on business models, which are not always compatible with patients' interests. With "medical bankruptcy" now an epidemic¹ and many people on fixed budgets choosing between food and medicine, the U.S. taxpayer is getting a bad deal.

We all agree that the present system of drug development and approval is unsustainable, especially in the era of "personalized medicine." Wood's proposals amount to clever posturing by an industry that is under well-deserved scrutiny. Other proposals that eliminate the profit motive,² at least in the early phases of development, deserve equal consideration.

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Dr. Frangioni reports having received research support from GE Global Research and having received lecture fees from MGI Pharma.

1. Himmelstein DU, Warren E, Thorne D, Woolhandler S. Illness and injury as contributors to bankruptcy. *Health Aff (Millwood)* 2005;Suppl Web Exclusives:W5-63–W5-73.
2. Frangioni JV. Translating in vivo diagnostics into clinical reality. *Nat Biotechnol* 2006;24:909-13.

THE AUTHOR REPLIES: I agree with Guda's comments and with most of Mayer's comments. However, in addition to the use of evidence-based medicine, we need to provide incentives for the development of the evidence base that physicians should follow. In the absence of comparative

studies, no evidence base can be created that will allow physicians to practice evidence-based prescribing.

Brown and Frangioni seem to have missed the point of my proposals. I am proposing that extended exclusivity, which is now offered to all new drugs regardless of their incremental benefit or true novelty, be offered only to truly innovative new therapies and the "me toos" that are shown to be safer or more effective than current therapies. Such a shift would have meant that many of the current "best-selling," most expensive drugs that have not been shown to be superior to older therapies would not have received extended exclusivity. The absence of extended exclusivity and the resultant lower prices would have produced huge savings for consumers and payers. Physicians should follow evidence-based prescribing practices, which do not support the prescribing of more expensive drugs with no proven additional benefit.

It is eye-opening to review the list of the 10 top-selling drugs and recognize how few of them show any evidence of superiority over generic drugs, even though billions of dollars are spent on them. This is truly an indictment of our prescribing practices. My proposals are designed to provide incentives for true innovation, in contrast to the current model, which rewards replication and molecular manipulation in order to extend the patent life of drugs. I would have thought that the creation of such incentives was a goal that we could all embrace.

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Tumor Necrosis Factor Inhibitors for Rheumatoid Arthritis

TO THE EDITOR: In reviewing the pathophysiological process of rheumatoid arthritis, Scott and Kingsley (Aug. 17 issue)¹ focus almost exclusively on dendritic cells and T cells. However, in mice, the maintenance of T-cell activation and tumor necrosis factor (TNF) production has been shown to be critically dependent on B cells.² Indeed, B cells appear to be pivotal in the pathogenesis of rheumatoid arthritis: they can be 10,000 times as potent as dendritic cells in presenting antigen,³ they form germinal centers in synovium, and they produce injurious autoantibodies.

The appropriateness of this recent shift in focus from T cells to B cells was borne out by a randomized, controlled trial reported by Edwards et al.⁴ The investigators found that patients who had active rheumatoid arthritis despite methotrexate treatment had a substantial improvement in disease symptoms 24 and 48 weeks after the depletion of B cells with rituximab (a monoclonal antibody against CD20) given either alone or in combination with cyclophosphamide or methotrexate.⁴ Furthermore, a single course of rituximab can significantly improve symptoms in pa-