Food and Drug Administration

More independent resources and ways to identify adverse events are key

Linda R Horton
partner
Hogan and Hartson, B-1040
Brussels, Belgium
lrhorton@hhlaw.com

Competing interests:

LRH advises drug companies on marketing authorisation, and compliance with US and European requirements for clinical trials, and post appraisal standards.

BMJ 2007;334:55-6
doi:

The Food and Drug Administration of the United States is now the patient on the examining table, with no shortage of attending doctors or nostrums. Months ago, the agency sought the advice of the National Academy of Sciences' Institute of Medicine on its drug safety system. The resulting report echoed previous suggestions that the agency should be given more money and power and proposed altering current industry approaches to drug development.[1-4] The drug industry, already smarting from tightened FDA drug safety standards, went into defensive mode.

The Institute of Medicine report will certainly play a key part in an upcoming debate in Congress over renewal of legislation that empowers the FDA to collect fees for a portion of the cost of reviewing applications for drug approval. The current user fee legislation expires on 30 September 2007 and must be reauthorised by then; this will provide a vehicle for new drug safety legislation if Congress decides it is necessary. With the recent US election results giving the Democratic Party control of both houses of Congress, it seems certain that the user fee extension law will include provisions to tighten drug safety law.

The current controversy is the latest in a series of drug safety crises. We could start with the infectious horse serum that led to the 1902 law on biologicals,

continue to the sulfanilamide tragedy that resulted in the 1938 law on new drugs, or look back on the horrors of thalidomide and how they led to the 1962 drug amendments. Drug safety issues are not new, and calamity often stimulates reform. The question is, what form it should take. So what are the key proposals made by the Institute of Medicine?

More resources? Flat line budgets coupled with increased costs have effectively eroded the agency's non-user fee base, including its drug safety pro-gramme. The majority of funds should come from taxpayers money as it is unreasonable to expect drug companies to bear a disproportionate share of the cost of monitoring product safety.

Separation of premarket evaluation of drugs from safety after marketing? This would dilute relevant expertise since two sets of experts would be needed for each stage. Other mechanisms are already in place to guard against loss of objectivity by those who originally recommend approval of a product. None the less, the proposal that each drug review team should include someone from the agency's drug safety office deserves attention and could easily be implemented.

More independence? The recommendation that the commissioner should have a six year term seems solid, although it would be difficult to force those who want to pursue other opportunities to stay. For example, Mark McClellan's departure after only a few months left the agency leaderless for a long period, during which Vioxx and other drug safety issues made head-lines. The FDA's status as part of the vast Department of Health and Human Services should also be re-examined. Surely the FDA is as important as other independent regulatory agencies like the Environmental Protection Agency and the Consumer Product Safety Commission.

Earlier and better communication? The idea that the FDA and drug companies should talk more, and sooner, about trial design and endpoints is laudable. Better understanding of regulations should help speed approvals and ensure earlier attention to safety signals. And European regulators need to join this dialogue. A potential problem is that the FDA is generally reluctant to be bound by its own early advice, and industry fears that the agency will take an excessively cautionary approach and recommend unnecessary studies. Both the FDA and drug companies need to find ways to pinpoint what testing will be needed for a given product or product class. Uncertainty about what it takes to win approval impedes development of useful products.

Authority for the FDA to order that manufacturers change the labelling of their products? This proposal is unnecessary because it underestimates the existing leverage that the FDA has at the pre-market stage. A company with an application pending before the FDA is desperate to get its product on the market and almost always gives in to agency requests on labelling. Even for a marketed product, the FDA can wield enormous power over a sponsor by threatening to publicise any disagreements about labelling.

Authority for the FDA to fine companies that fail to carry out the required post-market studies? This proposal deserves a closer look, but the agency only recently made full use of its existing and effective authority to publicise ("name and shame") those drug companies that had not kept promises to carry out post-market studies.

More authority in the area of adverse events? The reporting system for adverse reactions is fundamentally flawed. Although we cannot scrap such reporting systems as they do provide safety signals, we should pay more attention to well designed post-marketing studies, sentinel studies, patient registries, and other mechanisms that are better able to identify valid drug safety issues. Useful ideas are found in an International Conference on Harmonisation guidance document developed by the FDA and its European and Japanese counterparts (and industry in these three regions).[5]

More government funded studies of drugs? This idea is not new. I believe that large scale involvement of government in testing of drugs would be a mistake. Government needs to operate as a check and balance overseeing research done by others. If government is in charge of testing, the objectivity needed at the stage of data review will be lost.

In summary, additional resources for the FDA and alternatives to reporting of spontaneous adverse events would be key steps forward. The International Conference on Harmonisation should be used as a forum in which the FDA can collaborate with industry experts and international counterparts to develop harmonised approaches to drug safety, truly an issue without borders. The FDA recently indicated that it is sceptical about new initiatives from the International Conference on Harmonisation until it knows more about the implementation of previous ones.[6] This position is understandable, but the agency should avoid becoming isolated from other regulators or industry experts. The notion that the response to the drug safety crisis is a matter for the FDA and Congress only fails to consider the stake that people outside the US have in its outcome, and the global nature of the drug industry.

1 National Academy of Sciences, Institute of Medicine. *The future of drug safety: promoting and protecting the health of the public.* Washington, DC: IOM, 2006.

2 Wood A. A proposal for radical changes in the drugapproval process. *N Engl J Med* 2006;355:618-23.

3 Psaty B, Burke S. Protectingthe health of the public—Institute of Medicine recommendations on drug safety. *N Engl J Med* 2006;355:1753-5.

4 FurbergC, Levin A, Gross P, Shapiro R, Strom B.The FDA and drug safety. *Arch Intern Med* 2006;166:9.

5 Food and DrugAdministration. *Guidance for industry. E2E pharmacovigilance planning.* Washington, DC: FDA, 2006. www.fda.gov/cber/gdlns/ichpvp.htm.

6 FDA puts breaks (sic) on new ICH docs as itgauges industry interpretation. *FDA Week* 6 Oct 2006:7.