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Hard times at the FDA

The saying goes, "If it ain't broke, don't fix it." Given the recent spate of bad publicity surrounding the prescription drug approval process and subsequent drug monitoring by the US Food and Drug Administration (FDA), something is definitely 'broke'. At risk is public trust in the FDA and their assurances that prescription drugs are safe and effective.

In September 2004, the pharmaceutical giant Merck voluntarily withdrew its popular painkiller Vioxx after reports surfaced that it increased the risk of fatal heart attacks. The safety of other FDA-approved cyclooxygenase 2 (COX2) inhibitors has subsequently been questioned. Controversy now focuses on when knowledge of the serious side effects associated with these drugs became known and what steps, if any, the FDA took to protect the public. Critics claim the FDA has compromised its independence by becoming a servant to the pharmaceutical industry that it is responsible for regulating. However, such allegations are not new. An exposé published by *The Los Angeles Times* in December 2000 raised similar questions about the role of the FDA regarding other drugs that were approved but were later pulled off the market because of lethal side effects. That report quotes many FDA insiders who suggested their warnings about potential problems associated with new drugs under FDA review or during post-approval surveillance were ignored or suppressed by management. Angry US congressmen plan more hearings on how the FDA conducts its business after the testimony in November by one FDA scientist, David Graham.

Yet seeds for the scenario now unfolding were planted by Congress itself, partly in response to AIDS activists. Protesters claimed the FDA was too slow in approving new drugs, resulting in the death of hundreds for lack of effective drugs. Thus, in 1987 Congress enacted fast-track drug approval at the FDA, which considerably shortened the review period. Congress also passed the Prescription Drug Fee User Act of 1993 (reapproved in 1997 and 2002), which allowed the FDA to charge the applicant pharmaceutical companies fees to conduct expedited reviews. The pharmaceutical industry agreed to pay those fees, but only if the funds were used to review the new drug trials (using data supplied by the companies) within specified time frames; the fees could not be used to fund continued FDA monitoring of drug safety. Congress decreased FDA funding (in real terms), making it difficult to maintain its independent watchdog activities. This scenario set up an internal conflict within the branches of the FDA Center of Drug Evaluation and Research (CDER). To carry out the mandated reforms and to meet the user fee requirements, the 'revenue-generating' Office of New Drugs consumed an ever-larger share of the CDER budget, prompting the CDER to reduce support of its other units, including its Office of Drug Safety, which is responsible for post-approval drug surveillance. Thus, insufficient allocations have forced the FDA to 'raid' the post-approval safety studies unit to support its mandated fast-track pre-approval studies.

The rise and fall of the COX2 inhibitors is emblematic of the potentially negative consequences that these FDA policy changes engendered. Although COX2 inhibitors were granted fast-track approval in the late 1990s, subsequent clinical data have questioned both their efficacy and proposed benefits relative to those of pre-existing pain relievers. Several independent meta-analyses by the Mayo Clinic, the Kaiser Permanente health maintenance organization (HMO) and the US Veterans Administration found adverse health risks associated with COX2 inhibitors. Each of those institutions limited their use of COX2 inhibitors before the FDA warnings.

So the question remains why, if the FDA is mandated by Congress to protect citizens from harmful effects of unsafe drugs, it ignored early warning signs of significant risks associated with the new drugs. Certainly this question will be asked in future congressional hearings. FDA insiders, such as Graham, have noted pervasive pressure in the FDA to push new drugs through approval, even if hints of danger are detected. The FDA receives over 350,000 adverse drug reaction reports per year. Steven Galson, acting director of the CDER, stated in a 2003 *Frontline* interview that this figure represents only 1–10% of the actual adverse events that occur, because such reporting is not mandatory. Shifting budget priorities also prompted the CDER to slash funds for independent external reviewers, who previously did additional drug testing when such post-approval concerns were raised.

What is the prescription for the FDA to ensure drug safety? First, a strong independent commissioner is needed at the FDA, which has been represented by acting directors for much of the past 8 years. Congress should ensure sufficient funding exists for post-approval drug surveillance and trials. A standardized internet-based adverse-effect reporting system should be put into place. More extensive meta-analyses comparing drugs in the same class are also required. What is not so clear is who will fund them or whether the FDA is the agency to undertake these studies. With their large patient numbers and detailed clinical records, HMOs might be well situated, but cost-saving motives might influence their objectivity. The pending litigation over the COX2 inhibitors suggests that it might be in 'big pharma's' interest to fund such studies, helping them to avoid self-destruction, both financially and in the eyes of the public. The US Institute of Medicine, an arm of the US National Academies of Science, might provide both the independence and expertise required for such a role. An Institute of Medicine drug safety committee already exists, but its mandate is limited to review of medication errors, not the risks associated with drugs themselves. Changing this would be a good first step toward renewing confidence in the US drug safety assurance system.