

The US FDA at a Crossroads (HRG Publication #1780)

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The philosophy of one century is the common sense of the next.
Henry Ward Beecher (1813-1887)
American clergyman and reformer

Vioxx linked to heart attacks. Faulty pacemakers knowingly sold. Glucosamine ineffective. Plan B sacrificed to politics. Antidepressants cause suicidal thoughts. Crestor in trouble. These recent headlines paint a vivid picture of an agency in major disarray.

As longtime critics of the FDA, we at Public Citizen have often highlighted the agency's failures, including some of those listed above. But in casting a retrospective eye upon the FDA, it is critical not to lose sight of the agency's many accomplishments in its first 100 years and to make some suggestions for corrective actions in the future.

Referring to the period prior to the establishment of the then Bureau of Chemistry in 1906 as the snake oil era may seem unkind, but it is not far from the mark. Few nostrums were effective, and fewer still had actual evidence of efficacy. Unrestricted claims of magical cures burst from the pages of newspapers and magazines, to the point that some of the most bellicose voices opposing advertising restrictions on drugs emanated from the publishing industry.

It took Upton Sinclair's *The Jungle*, with its revelations of the appalling conditions in the meat-packing industry, and other less-heralded exposes in *Collier's* and *Ladies Home Journal*, to usher in the *Pure Food and Drug Act* of 1906. The Act established the Bureau of Chemistry as the first US regulatory agency.

Even at the time, the Act's requirements seemed transparently weak. Although drugs containing morphine, chloroform, marijuana or the like had to be labelled, there was no requirement to list other active ingredients. A section of the Act precluded false effectiveness claims; it fell victim to the poor science of the times when courts ruled that such claims could not be adjudicated because available scientific evidence was so lacklustre. Foods could not be adulterated according to the Act, but Congress appropriated literally nothing for enforcement. Nonetheless, the Act established the agency, and its jurisdiction was defined.

It is a truism of US food and drug law history – indeed, of US laws in general – that little changes without a disaster of significant proportions. And the disasters most likely to awaken a slumbering Congress are those that affect children. The next major drug-related legislative development, the 1938 *Food, Drug, and Cosmetic Act*, was the direct result of at least 107 deaths, many in children, due to ingestion of a liquid preparation of the antibiotic sulfanilamide that contained the coolant diethylene glycol.

The 1938 Act was groundbreaking in at least two respects. First, it was the first law anywhere in the world to require regulatory approval before a drug could be marketed. Second, it required that a drug be proved *safe* before it could be sold. Countries around the globe rushed to adopt similar statutes.

Another drug disaster involving children – phocomelia (short arms or legs) in newborns due to maternal ingestion of thalidomide – generated the political will to pass the next meaningful drug regulatory reform. Unlike in many European countries, thalidomide was not approved in the US. Nevertheless, the 1962 *Kefauver-Harris Amendments* to the *Food, Drug, and Cosmetic Act* required, again for the first time anywhere in the world, that drugs be proved both *safe* and *effective* before they could be marketed. Companies that introduced drugs into the market between 1938 and 1962 would have to provide evidence (usually in the form of new clinical trials) to demonstrate their product's safety and effectiveness; those marketed prior to

1938 were grandfathered in. As a result, hundreds of drugs from the 1938-1962 period were banned and untold numbers of drugs have never entered the US marketplace at all.

In this history, one can readily discern a pattern of gradually escalating levels of regulation. Drug approval stood increasingly on scientific grounds, evidence was substituted for anecdote and groundless claims of safety and efficacy were thrown out. As Beecher probably would have concurred, that philosophy has come to seem like common sense.

There have been relatively few important drug or device statutes passed since that time. The *Medical Device Amendments* of 1976 brought some semblance of regulation to this still under-regulated area; the *Hatch-Waxman Act* of 1984 eased the passage of generic drugs to market; and the *Food and Drug Administration Modernization Act (FDAMA)* of 1997 included a series of relatively minor changes to existing law on conflict-of-interest disclosure and off-label promotion.

However, an apparently modest statute passed in 1992 – the *Prescription Drug User Fee Act (PDUFA)* – has had major reverberations throughout the agency. The Act permitted the FDA to charge pharmaceutical companies for the review of their drugs – a seemingly innocuous pay-as-you-go attempt to adequately fund a chronically cash-starved agency. In our view, this arrangement presents an irresolvable conflict of interest in which FDA regulators are expected to police their funders. Today the agency collects about a quarter of a billion dollars annually in user fees, about one-half of all expenditures on drug review. The user fee concept has now been extended to the device, biologics and veterinary drugs centres within the FDA. The result has been a fundamental change in the ambience within the agency in which pharmaceutical companies are increasingly seen as stakeholders, customers or even clients. Former FDA Commissioner Mark McClellan's speeches often echoed the familiar drug industry line about the need to maintain prices, and hence profits, at high levels in order to spur research. If you pay them, it seems, they will listen.

The agency's current ills are manifold: an 85% decline in drug advertising enforcement between 1998 and 2004; staff disillusionment and turnover far in excess of that in most other federal agencies; internet-based drug sales that are essentially beyond the agency's control; direct-to-consumer advertising that consigns physicians to the sidelines while converting patients into the companies' marketing agents; counterfeit medicines flooding the market, in part because the agency took 18 years to enact regulations to track drugs through the distribution chain; requirements to conduct postmarketing studies openly flouted by the pharmaceutical industry; and declining public confidence that the agency is ensuring the safety and efficacy of new prescription drugs.

From a philosophical perspective, the most fundamental change may be the assault on rationality, the basis upon which the agency was founded, that justified the various expansions of its mandate and that made it a global pioneer. Disagreements within the agency, the very essence of scientific discourse, are met with stern opposition and bureaucratic isolation. In a study we conducted in 1998, medical officers identified at least 27 drugs approved in the previous three years for which they had recommended non-approval. About a dozen drugs have been removed from the market since 1997, an unprecedented number for such a short period of time. Many had shown the toxicities for which they were later banned in pre-approval clinical trials. The near-total absence of Congressional oversight means that more drug safety disasters loom.

FDAMA also provided for expedited drug review and approval on the basis of a clinical or surrogate endpoint that is "reasonably likely . . . to predict clinical benefit" if the drug is for a serious or life-threatening condition. The law also required companies to conduct a postmarketing study to establish the efficacy of such drugs with respect to a hard endpoint (such as morbidity or mortality) and empowered the FDA to withdraw approval "if a postmarketing clinical study fails to verify clinical benefit". Yet, after four randomised trials demonstrated that the lung cancer drug Iressa had no impact upon mortality or quality of life, the drug remained on the market, potentially diverting patients from an approved drug with known effectiveness with respect to hard endpoints. Meanwhile, the editorial page of the *Wall*

Street Journal, carries articles mounting an assault on randomised, controlled trials and the efficacy standard itself.

Irrationality is not confined to the drug arena. The vagus nerve stimulator (VNS) is surgically implanted at the base of the neck, where it generates periodic electrical pulses stimulating the vagus nerve. A randomised, placebo-controlled trial for patients with so-called treatment-resistant depression showed no statistical evidence of benefit after three months of therapy. Yet, the device was approved based on long-term data using a separately recruited, non-randomised, unblinded comparison group. A Senate Finance Committee investigation later found that every one of the more than 20 medical officers, scientists and management staff in the FDA's drug and device divisions who were consulted opposed VNS approval. The FDA's device centre director, Daniel Schultz, overrode them all.

In other areas, FDA regulation has reverted to pre-1938 levels. Thanks to the *Dietary Supplement Health and Education Act* of 1994, dietary supplements are now clearly regulated as foods, rather than drugs. The consequences? No requirement to prove safety or efficacy, no need to register your product with the FDA, no banning of dangerous supplements unless they exceed a very high threshold and no mandatory reporting of adverse events. Even claims that are considered "structure/function" (eg, "promotes prostate health") are permitted as long as they don't cross the line, inscribed in invisible ink apparent only to industry and FDA lawyers, into health claims (eg, "treats the symptoms of an enlarged prostate").

The practice of pharmacy compounding has been similarly rescued from obscurity by *FDAMA* provisions exempting compounded drugs from having to demonstrate safety or efficacy. As is inevitably the case, entrepreneurs rapidly fill the void with unsustainable claims and hazardous products. Three patients were killed and ten hospitalised when compounded betamethasone, contaminated with the bacteria *serratia*, was injected into their spinal columns.

As the FDA flirts increasingly with departures from the scientific method that underpinned all the agency's successes in the past century, a host of reforms are necessary. We will mention but four. First, PDUFA should be repealed to end the conflict of interest inherent in accepting industry funding. Second, the FDA should be granted authority to levy civil monetary penalties in the drug safety/efficacy arena. This prerogative makes sense for an agency with authority over literally one-quarter of the US economy. Its current inability to levy fines allows companies to brazenly defy the agency's insistence that companies conduct post-marketing studies because they know the agency would never take the draconian step of removing the drug in question from the market. Third, a drug safety unit with direct access to the FDA commissioner must be established. FDA's current plan to house this group within the Center for Drug Evaluation and Research maintains the current conflict of interest in which those who may have erred in approving a drug have to decide whether to withdraw it.

Finally, new drugs in crowded therapeutic classes should be required to demonstrate some advantage in safety and/or efficacy over existing drugs before approval can be secured. This is the logical extension of the historical widening of FDA requirements – from labelling to pre-approval demonstrations of safety to proof of safety and efficacy. The great majority of the recent drug disasters have occurred among "me-too" drugs – drugs that are only minor chemical modifications of already approved drugs. For clinicians to base their decisions upon simply knowing that these drugs work better than nothing at all, rather than on how they stack up to their competitors, defies common sense.

Peter Lurie, MD, MPH is the Deputy Director of Public Citizen's Health Research Group.

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