Written by **Michael Tennant** on September 16, 2010

The FDA: Neither Safe nor Effective

Once upon a time, so the story goes, the American pharmaceutical industry was a "wild West" in which greedy, unscrupulous snake-oil salesmen preyed on unsuspecting citizens. Average Americans, in the same tale, were incapable of sifting through the claims of drug purveyors and of determining which drugs were both safe and effective, and thus were suffering and dying in droves at the hands of these conniving profiteers. The happy ending to the story is that the federal government, in response to public outcries for salvation, stepped in and forced all drug manufacturers to prove their products were safe and effective before they could sell them; henceforth, Americans could be certain that no drugs would ever harm them again.

Would that it were so simple. In fact, say economists Daniel B. Klein, Ph.D., and Alexander Tabarrok, Ph.D., not only is the back story in that familiar yarn sorely lacking an historical basis, but the very idea that federal premarket approval of drugs is beneficial is also greatly in doubt.

Klein and Tabarrok are the authors of an Independent Institute project called FDAReview.org that examines the question "Is the FDA safe and effective?" The two men conclude that it is neither, writing that "FDA control over drugs and devices has large and often overlooked costs that almost certainly exceed the benefits" and that "FDA regulation of the medical industry has suppressed and delayed new drugs and devices, and has increased costs, with a net result of morbidity and mortality."

They do not, however, place the majority of the blame on the FDA itself but rather on the legislation that created the FDA and has steadily expanded its duties and powers. The FDA's initial responsibilities were small and relatively innocuous; as Congress has piled more mandates onto the agency, its delays have increased and its effectiveness has decreased.

The Evolution of Regulation

Klein and Tabarrok begin their study with a detailed overview of the history of federal drug regulation. They write that "before the twentieth century there was no direct federal regulation of drugs or other consumer products," yet somehow Americans managed to survive and prosper just the same.

While it's true that the pharmaceutical industry was also relatively small prior to 1900, with most drugs being mixed by hand at local pharmacies, pharmacists and doctors had already undertaken to improve the safety and quality of the drugs being sold to consumers. For example, in 1820 the *U.S. Pharmacopoeia* was created. "A private, voluntary undertaking of physicians, pharmacists and colleges of pharmacy, the *USP* presented a formulary of compositions and listed chemical compounds, crude drugs, fixed oils, and other substances typically kept by a pharmacist," explain the authors. "Later the

USP listed tests for determining purity. Leading pharmacists regularly revised the *USP* as new and better drugs, compositions, and tests were discovered and created." The American Medical Association and the American Pharmaceutical Association were formed; the latter began publishing the *National Formulary*, whose function is "to provide standards for drugs omitted from the *USP* and to serve as a proving ground for drugs eventually transferred to the *USP*," in 1888. In short, long before the FDA was even a gleam in Uncle Sam's eye, the pharmaceutical industry was regulating itself.

Klein and Tabarrok point out that crises have played a large part in Washington's increasing control over the pharmaceutical industry. The very first significant federal drug regulation, the Biologics Act of 1902, was passed in the wake of a vaccine contamination scare. The act, write the economists, "required that federal government grant premarket approval for every biological drug and for the process and facility producing such drugs. Never before had such premarket control existed in the United States."

Four years later the Pure Food and Drugs Act was passed, again as a result of a crisis mentality, though this time the crisis was largely imagined. Between muckraking journalism (for example, Upton Sinclair's *The Jungle*) and the publicity stunts of federal Bureau of Chemistry Chief Harvey Washington Wiley (who had a tendency to seek federal regulations to benefit his cronies in the business world), the public was led to believe that they were in grave danger of contaminated food and drugs.

The resulting law still did not give the federal government the power to prevent drugs (other than biological drugs as provided for in the 1902 law) from coming to market. In fact, it largely affirmed the industry's self-policing, recognizing the "*U.S. Pharmacopoeia* and *National Formulary* as official standards for the strength, quality, and purity of drugs and for the tests to make such determinations," according to Klein and Tabarrok. It also prohibited "misbranding" of drugs, defined as failing to indicate the quantity or proportion of certain potentially dangerous or addictive drugs.

Klein and Tabarrok thus conclude: "For consumers, the main result of the 1906 law was not to restrict choices but to provide more information.… Because the feds could not wield coercive premarket power, the Chemistry Bureau and industry trusted each other and cooperated to improve drug manufacturing."

The regulatory duties of the Chemistry Bureau having been transferred to the Food and Drug Administration by 1930, the next step was to increase the FDA's power even further. Since, as Klein and Tabarrok note, "the Constitution does not give the federal government any power to regulate drugs," the Food, Drug, and Cosmetic Act of 1938 abused the interstate commerce clause to permit federal regulation of drugs. The law required manufacturers to file a New Drug Application (NDA) with the FDA for each new drug they wanted to bring to market, after which it was up to the FDA either to approve or to deny the application, although, say the authors, "the default position was approval … and as a result the costs of the FDA to the public were kept low." In addition, the law "had the effect of creating a new class of prescription-only drugs" and "expanded the FDA's powers over medical devices."

After that the mandates and accompanying regulations just kept coming. Nearly all of the laws expanded the FDA's mission, most especially the 1962 Kefauver-Harris Amendments (passed in the wake of the thalidomide tragedy), which authorized the FDA to require proof of efficacy for all new drugs before they could go to market. A few attempted to rectify some of the unintended consequences of earlier legislation. The resulting centralization of decision-making for the pharmaceutical and medical-device industries reduced patients' and doctors' choices and greatly delayed the bringing of new products to market.

Regulatory Harm

Klein and Tabarrok spend a significant amount of time going into detail about the harm that the FDA's approval process visits on ailing Americans. They point out that there are at least two negative effects of the extensive testing the FDA requires:

> First, it delays the arrival of superior drugs. During the delay, some people who would have lived end up dying. Second, additional testing requirements raise the costs of bringing a new drug to market; hence, many drugs that would have been developed are not, and all the people who would have been helped, even saved, are not.
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> In addition, because FDA approval is mandatory, industry and medicine must heed FDA standards regardless of their relevance, efficiency, and appropriateness. Not all testing is equally beneficial. The FDA apparatus mandates testing that, in some cases, is not useful or not appropriately designed. The case against the FDA is not that premarket testing is unnecessary but that the costs and benefits of premarket testing would be better evaluated and the trade-offs better navigated in a voluntary, competitive system of drug development.

As mentioned above, the Kefauver-Harris Amendments of 1962 were something of a watershed in the history of federal drug regulation. Now drug companies had to prove not only that their products were safe but also that they were effective.

Yet both safety and efficacy vary with the individual patient and his circumstances. A drug to treat one ailment may be safe for an otherwise healthy person but could be deadly for someone who is already suffering a variety of other maladies. Furthermore, a person who is suffering from a terminal illness may be willing to bear the risk of a drug the FDA deems unsafe in hopes of curing his illness or at least improving the quality of his remaining life. Efficacy, too, comes down to an individual situation. Some drugs work on some people and not on others, while others, perhaps not as efficacious as the FDA deems necessary for approval, are sufficiently helpful to some individuals (or at least better than no treatment at all).

The authors cite a 1973 study by Sam Peltzman to demonstrate that the Kefauver-Harris Amendments have done little good and much harm. Peltzman developed a model that forecast the annual number of new drug introductions both pre- and post-1962. The model worked beautifully pre-1962, tracking the actual number of new drug introductions quite accurately. However, once the 1962 amendments went into practice, the model, using the same criteria that had succeeded prior to 1962, consistently predicted a much higher number of new drug introductions than actually occurred. It can be inferred that, in the absence of Kefauver-Harris, many more drugs would have been introduced each year than actually were. In fact, write Klein and Tabarrok, "the average number of new drugs introduced pre-1962 (forty) was also much larger than the post-1962 average (sixteen)." Thus, they conclude that "the 1962 Amendments caused a significant drop in the introduction of new drugs."

Furthermore, because the costs of FDA regulations are the same regardless of whether a drug is intended to treat a common ailment or a rare one, say the economists, "millions of Americans have few or no therapies available to treat their diseases because of increased costs of drug development brought about by stringent FDA 'safety and efficacy' requirements." Although Congress tried to remedy this situation with still more tinkering with the system via the Orphan Drug Act of 1983, the good doctors suggest that it would even "be better to reduce or eliminate FDA regulations for all drugs and patient populations."

Klein and Tabarrok attempt to quantify the number of lives lost owing to FDA delays and the reduction in new drug introductions. They write that "Gieringer (1985) estimates the loss of life from delay alone to be in the hundreds of thousands." Meanwhile, the extra time required for approval by the U.S. government versus European governments, known as drug lag, has resulted in "hundreds of thousands" of deaths over the years. Therefore, they say, the "conclusion is clear: the FDA is responsible for more lives *lost* than lives *saved*."

They also take on the issue of "off-label" uses of drugs, i.e., prescribing a drug for uses other than those for which the FDA approved it. These off-label uses are discovered through private-sector testing, research, publications, and so on, not through the centralized FDA process. Nevertheless, doctors and patients are more than willing to make use of these non-FDA-approved treatments. Thus, the authors conclude that the "off-label market … provides a good idea of the benefits to be had from reducing FDA control over approval decisions." Moreover, they add: "Efficacy requirements should be dropped altogether!" These fellows don't mince words.

They are similarly direct in summarizing their findings with regard to the harm caused by FDA regulations, saying, "All the systematic evidence goes against the coercive FDA apparatus."

One might at this point ask why it takes the FDA so long to approve new drugs. The obvious answer is simple bureaucratic inertia, and that certainly explains some of it. However, the larger reason is that approving a drug that is later found to be unsafe leads to bad publicity for the agency, while failing to approve (or delaying approval of) a valuable drug generates no such news. After all, few people outside the FDA will know if a worthwhile new drug is delayed or never sees the light of day, but everyone will find out if an FDA-approved drug causes illnesses or deaths. As a result, the tendency among regulators is always to err greatly on the side of caution. The authors quote an anecdote from physician, Hoover Institution fellow, and former FDA employee Henry I. Miller that perfectly encapsulates this mindset:

> In the early 1980s, when I headed the team at the FDA that was reviewing the NDA for recombinant human insulin, … we were ready to recommend approval a mere four months after the application was submitted (at a time when the average time for NDA review was more than two and a half years). With quintessential bureaucratic reasoning, my supervisor refused to sign off on the approval — even though he agreed that the data provided compelling evidence of the drug's safety and effectiveness. "If anything goes wrong," he argued, "think how bad it will look that we approved the drug so quickly."

As shown earlier, such delays in approving drugs — and, worse, complete denials of approval — can cost countless lives. But since these victims never make the news, the FDA has every incentive to continue its current practices.

Having laid out their compelling case against the FDA, Klein and Tabarrok turn their attention to options for reforming the system.

Recommended Reforms

The first suggested reform is for the FDA to provide more information to consumers about the drugs that are available. They point out that consumers "can and should ask for product labels with their prescriptions" and that the "FDA should also pay more attention to designing labels that can be easily read and understood," in contrast to longstanding practice whereby it is assumed that consumers are too ignorant to understand accurate drug labels and should therefore defer to the received wisdom of their physicians and the FDA. Furthermore, the economists recommend a "split-label regime" whereby

"the product label would consist of a part for FDA-approved health and nutrition claims and a part for 'Not FDA Approved' claims." This approach is already working well for dietary supplements and could work equally well for drugs.

"As of 2008 the FDA may deny seriously ill patients — those facing morbidity or death from their illnesses — the use of unapproved drugs," write Klein and Tabarrok. "This FDA intervention has resulted in incidents where physicians were unable to provide experimental or unapproved treatments despite the terminal nature of their patients' illnesses." They recommend passage of the "Access, Compassion, Care and Ethics for Seriously Ill Patients Act," which was introduced in the Senate by Sen. Sam Brownback (R-Kan.) in 2008 but never got out of committee. While far from perfect, the bill does give seriously ill patients and their doctors the option to choose riskier treatments and protects drug companies from subsequent lawsuits.

A third recommendation is to adopt Henry Miller's proposal, to wit: Nongovernmental drug-certifying entities would compete in the free market for hire by pharmaceutical companies to oversee drug development and testing. If the hired body certified a new drug, the certifier and the drug company would together present the NDA to the FDA, which would then have 90 days to respond. Failure to respond would constitute automatic approval — a welcome return to a portion of the pre-1962 state of affairs.

Klein and Tabarrok also suggest that the "U.S. government should establish reciprocity with countries that have a proven record of approving safe drugs — including most west European countries, Canada, Japan, and Australia." This, they say, would "eliminate the FDA's monopoly on drug approval" because foreign drug companies whose products have already been approved in their own countries could then immediately market them in the United States, and U.S. drug companies would have the option of taking their drugs to foreign governments for certification, knowing that approval in, say, Great Britain would mean automatic approval in the United States.

They next suggest, as they had explicitly stated earlier, that the proof-of-efficacy requirement be completely eliminated since "there is strong evidence that private enterprise and tort law takes [sic] care of efficacy and that the costs, delays, and drug loss from FDA efficacy requirements are unredeemed." "That simple reform," they explain, "would greatly expand the range of drugs developed (in particular for rare diseases), increase the speed with which they get to market, and significantly reduce costs and drug prices."

The final reform short of complete freedom that the authors suggest is simply to make FDA drug testing and approval optional. This, they aver, would quickly prove whether healthcare providers and patients actually value the FDA's seal of approval or merely submit to its approval process because they have no choice. Of course, as they point out in a sidebar, if this reform were enacted, "the FDA would probably sink like a stone, and FDA officials know it," which explains their opposition to any and all liberalization.

After discussing these potential reforms, Klein and Tabarrok then describe their ideal reform, which they term the "Sensible Alternative," defined as "a voluntary system in which private firms, organizations, and perhaps also other governments and a voluntary FDA assured consumers of drug safety and efficacy." "Careful reflection," they argue, "will show that the combination of voluntary practices and the tort system are well able to meet the demand for quality and safety assurance."

They then describe in some detail three parts of their voluntary system that they believe will help assure both quality and safety in pharmaceuticals.

First is the seller's reputation. A drug company with a track record of selling safe, effective drugs will garner both repeat and new business. A company that sells unsafe or ineffective drugs will face losses, a fact of life that Johnson & Johnson is learning the hard way at present. Having recalled millions of units of Tylenol, Motrin, and Benadryl over the past year, the company is now facing a perhaps permanent loss of business to less expensive and safer store-brand equivalents, according to an August 6 CNN report. Consumers have discovered that they can get by just fine with the store brands, and they may be wary of returning to the brand-name drugs that have proved less than safe. Will they also become less willing to purchase other Johnson & Johnson products? Only time will tell.

Second on Klein and Tabarrok's list is "knower organizations." A knower organization is a "private organization that knows more than the consumer about a seller's reputation or about the quality and safety of the seller's products." Knower organizations "often inspect quality and safety, and grant a certification mark or seal of approval." Among existing knower organizations are *Good Housekeeping*, Underwriters' Laboratories, Moody's, and the American Dental Association. Knower organizations "may investigate quality and safety, and sell their reports directly to consumers"; examples include the ECRI Institute (which evaluates medical products for hospitals, HMOs, and government agencies), *Consumer Reports*, credit bureaus, and doctors and pharmacists. There would, the economists argue, be many more such organizations if not for the existence of the FDA, which most individuals and businesses take for a knower organization when in fact it is a bureaucratic permission granter.

Third, the authors cite middlemen, from pharmacies to pharmaceutical companies to HMOs, as those who have strong profit incentives to ensure that drugs sold to the public are safe and effective.

Finally, Klein and Tabarrok suggest a thought experiment. What if someone proposed that there be a federal agency that had complete authority over what electronic products could be brought to market? Most people would quite correctly find that absurd because the market already has many built-in safeguards to ensure that electronics are safe. Yet this is precisely the regime under which Americans are forced to live when it comes to drugs and medical devices.

Drs. Klein and Tabarrok have performed an outstanding service by collecting in one place the many disparate studies on the harm done by the FDA and, further, by suggesting both partial reforms and, ultimately, their sensible alternative, which is to say, freedom.

In their 1993 book *Freedom of Informed Choice: FDA Versus Nutrient Supplements*, Durk Pearson and Sandy Shaw quoted their correspondence with the late Nobel Prize-winning economist Milton Friedman (one of many such quotations on FDAReview.org), summing up the project's conclusions quite nicely: "'The FDA has already done enormous harm to the health of the American public by greatly increasing the costs of pharmaceutical research, thereby reducing the supply of new and effective drugs, and by delaying the approval of such drugs as survive the tortuous FDA process.' When asked, if you could do anything to improve health in America, what would you do? Friedman replied: 'No more licensing of doctors. No more regulation of drugs. Not of any kind. Period.'"

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