

A risk-averse FDA is not good for Americans' health.

Type I Terrors

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The U.S. Food and Drug Administration regulates the nation's pharmaceuticals, medical devices, cosmetics, and most of its foods. Weighing risks and benefits is the agency's stock in trade, but those judgments should be focused on benefiting the public, not itself. Unfortunately, the FDA's self-interest has caused soaring risk aversion, escalating development costs; and fewer new products available to consumers.

The FDA's trend toward unreasonable — some would say fanatical — risk aversion began two decades ago under the influence of then-agency head David Kessler. However, it has escalated markedly in the first two years of the Obama administration. The numbers of clinical trials and patients that support applications for marketing approval, and the length and complexity of the trials all have been on the rise. Regulators have even introduced new criteria for the marketing of drugs, in addition to safety and efficacy regulations mandated by statute. As a result, the cost to bring a single drug to market now averages more than \$1.4 billion and requires 12 to 15 years. Only two in 10 drugs that are finally approved recoup their development costs.

TOO RISKY

Science takes a back seat to political correctness and bureaucratic capriciousness at today's FDA. To see this, consider a few examples of some products that the agency has determined are too risky:

E-cigarettes The FDA warned last year about the safety of a product called the "electronic cigarette," a substitute for smokers who are trying to quit. These "e-cigarettes" look like traditional cigarettes and supply users with vaporized nicotine, some even boasting an LED light at the tip to simulate combustion. These products contain little or no tobacco and are non-combustible, and they lack most of the risks of smoking.

For the vast majority of smokers unable to quit even with the help of drugs and counseling, e-cigarettes could be a life-

saver. But after performing a cursory laboratory analysis of the products, regulators warned smokers to avoid them, essentially telling them to stay with deadly cigarettes.

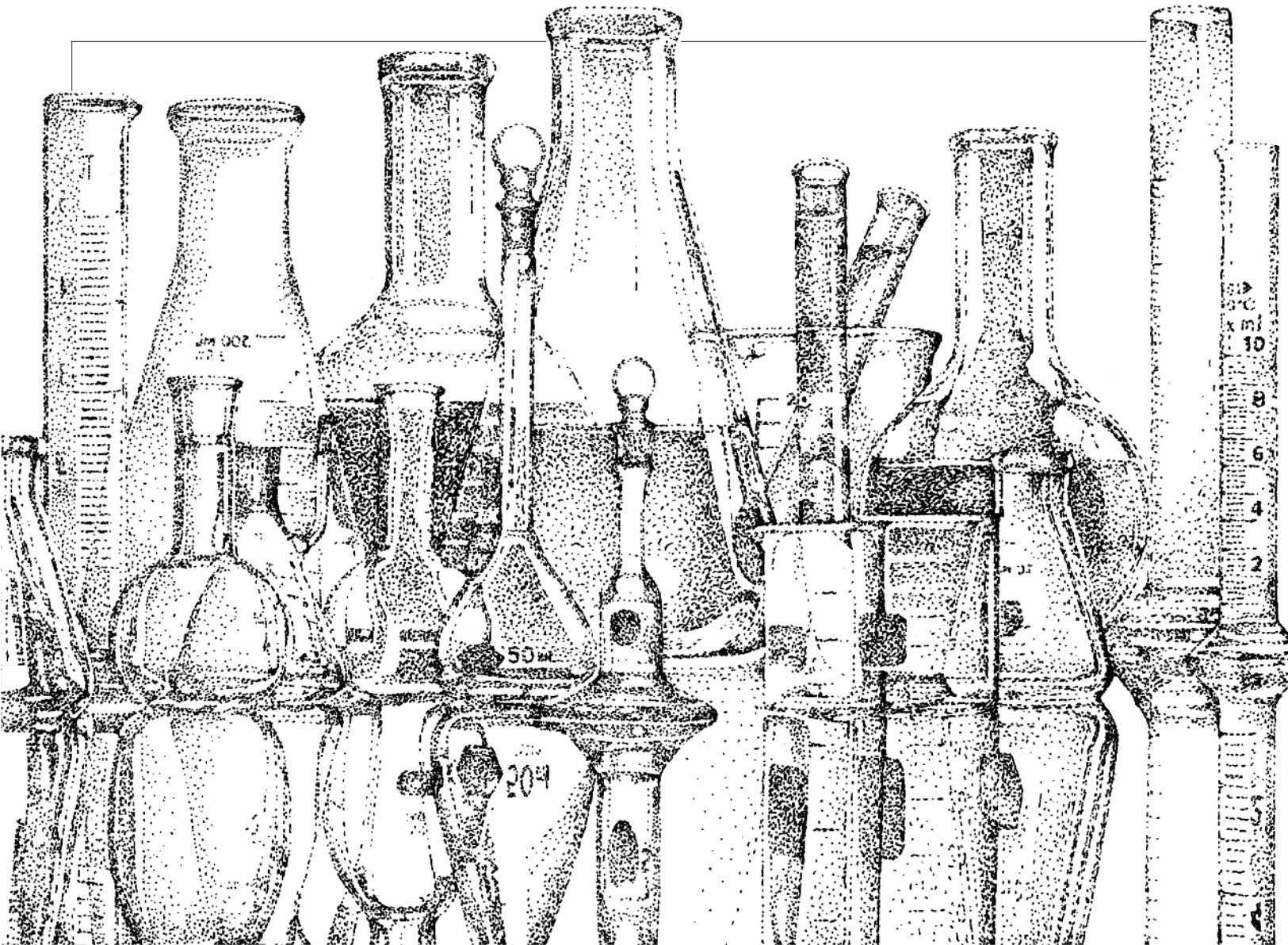
The FDA's analysis was performed on only "a small sample of cartridges from two leading brands of electronic cigarettes," which "contained detectable levels of known carcinogens and toxic chemicals to which users could potentially be exposed." The FDA highlighted the finding of diethylene glycol, an ingredient used in antifreeze. In fairness, the presence of this chemical is a concern. However, it was detected in just one of the 18 cartridges that the agency tested. Moreover, the FDA reported that five cartridges contained "very low levels" of tobacco but did not say exactly how low, nor is there any indication whether these trace amounts would pose a measurable risk to users of the products.

What is most frustrating about the FDA's decision on e-cigarettes is that the agency has approved other smoking cessation products that contain nicotine and detectable levels of known carcinogens (a byproduct of obtaining nicotine from tobacco), and other smoking cessation aids have significant side effects. FDA regulators appear not to grasp the concept of comparative risk assessment. Conventional cigarettes are, after all, a major killer of Americans, accounting for approximately 30 percent of cancers, so any product that could help smokers to quit would be a boon to public health.

Gabapentin In February, the FDA turned down a new formulation of a popular drug, gabapentin, for the treatment of restless leg syndrome, the uncontrollable movement or twitching of the legs caused by an imbalance in the neurotransmitter dopamine in the brain. In a "complete response" letter, which is issued by the FDA to a drug sponsor to deny approval after its review of the application for marketing approval is completed, the agency expressed concern about the finding of pancreatic tumors in a rat study of the drug.

Two things are problematical about this decision: First, the FDA knew about similar findings in animal testing of the drug when they approved the original formulation more than a decade ago for uncontrolled epilepsy (but rationalized that approval because of the seriousness of the condition). One wonders, then, why regulators permitted the drugmaker to plan and perform the clinical trials for the new formulation

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if the agency already had scientific data on the drug's risks that would prevent its ultimate approval.

Second, rats are not little people with beady eyes and long tails. As the American Council on Science and Health has pointed out, "Differences in physiology and anatomy between humans and mice, rats, and other species often make it difficult to apply animal results confidently and directly to human health. Animal testing should not be viewed as sufficient, in the absence of additional supporting data, to predict risk to humans." There are no additional supporting data on gabapentin that offer any hint of causing tumors in humans. (See "Regulating Unknown Risks," Spring 2010.)

Rotarix In March, the FDA asked pediatricians to stop administering Rotarix, a vaccine made by GlaxoSmithKline that prevents rotavirus infection, a diarrheal illness that can cause severe dehydration. The rationale was that small amounts of DNA from a pig virus had been detected in the vaccine preparation. That might sound like a good reason for concern — except that the FDA itself confirmed "that the material has been present since the early stages of product development, including during clinical studies." In other words, all of the studies that confirmed the safety and efficacy of the vaccine

were performed with the viral DNA present. Moreover, the FDA averred that "extensive studies, including placebo-controlled, randomized clinical studies involving tens of thousands of vaccine recipients, support the safety and effectiveness of the vaccine." The head of the agency, Margaret Hamburg, even announced, "We're not taking this action on the basis of a safety concern." She failed to state what type of concern *was* the basis for the action.

Finally, consider this: the virus is commonly consumed in pork products and does not cause disease in any known host, including humans. One must wonder, then, what the problem was that the FDA was trying to fix by interrupting the use of the vaccine.

The story gets better: Regulators withdrew Rotarix from the market, in part, because of the availability of an alternative vaccine, Rotateq, produced by Merck. But using a new, high-sensitivity assay, Merck soon thereafter detected DNA fragments from two pig viruses in its vaccine. So did the FDA also take the Merck drug off the market? No — it rescinded its order on the GlaxoSmithKline drug. So, are the drugs safe or unsafe? And did the FDA make its decisions in order to protect public health, or the FDA?

This bumbling over the vaccines is not without side effects.

It will fuel the hysteria of the anti-vaccine activists and some parents will be sufficiently confused that they will delay vaccinating their children. Regulators have thereby created a wholly gratuitous public health problem.

Even salad dressing There are other recent examples of the FDA's over-reaching and over-reacting. Last year, Chicago federal appellate Judge Richard Posner blasted the government for bringing a case against a salad dressing wholesaler who had changed the labels on 1.6 million bottles of salad dressing to extend their "best when purchased by" date. The wholesaler did this because the salad dressing is considered "shelf stable," and there really is no date on which the product would be considered to have expired. Moreover, there is nothing in the law or regulations about "expiration" or "best when purchased by" dates on food labels. The Department of Justice nonetheless brought criminal proceedings at the direction of the FDA's Office of Criminal Investigations, which argued that it is a federal crime to change a "best when purchased by" date on the label of any food product without regulators' approval.

Judge Posner wrote that for a criminal case to be prosecuted, a requirement about dates on food labels has "to be found in some statute or regulation, or at least in some written interpretive guideline or opinion.... It is a denial of due process of law to convict a person of a crime because he violated some bureaucrat's secret understanding of the law." Posner found that not only was there nothing in food law about "best when purchased by" dates, but that there was little likelihood of endangerment of public health. Finally, he read the riot act to both the prosecutor and the "expert" witness from the FDA; of the latter, he said, "the testimony of the FDA's employee was not just improper and inadmissible but incoherent." That's our tax dollars at work.

MEDICAL DEVICES

Medical devices are something of an orphan sister to the more glamorous drugs, but they include some of the genuine miracles of modern medicine: pacemakers, artificial joints, cardiac stents, scanners, and radiotherapy machines. For decades, many devices have received FDA approval via a fast-track process called 510(k), which is designed for products that are similar to earlier products, known as predicate devices. Although admittedly the link between the new product and the predicate device has sometimes been tenuous, about 3,500 devices are approved annually via this mechanism, with extremely few problems.

The FDA has made it clear that qualifying for the 510(k) pathway will in the future become more difficult and that more data will be required for the standard pathway. These new requirements threaten innovation in the industry, especially at a time when financing is hard to obtain. Unlike the drugs sector, many medical device makers are small and financially fragile. Device companies have begun to move abroad and even to write off the U.S. market for certain products that they consider to be over-regulated.

Another dubious policy decision concerning medical

devices is the FDA's announcement that it is reconsidering a long-standing, successful policy that permits nongovernmental "accredited persons" to perform reviews of certain low or moderate risk products. (Final approval is still up to regulators.) This revision would be yet another example of the trend toward more stultifying, expansive, and expensive regulation that is slowing innovation and endangering developers of both drugs and medical devices — and the patients who need their products.

The "accredited persons" policy, which has been in place for 13 years, is a more limited, more conservative version of a policy that has worked effectively for decades in Europe, where oversight of medical devices (as well as many other consumer products) relies heavily on product standards rather than on the primary evaluation by bureaucrats. In the U.S. version, products such as blood pressure cuffs, wheelchairs, root canal filling resins, and various kinds of scopes used to visualize joints and other structures may receive initial review from third parties. The third-party route for clearance in the United States is about 33 percent faster than for similar applications that go directly to the FDA and is generally regarded as a regulatory success story — except by federal officials.

Arguably, instead of terminating third-party review of certain medical devices, the program should be expanded to include at least some drugs. A viable model for the evaluation of clinical data by independent reviewers already exists: In a two-year pilot program (1992–1994), the FDA contracted out to a nonprofit technical consulting company, the Mitre Corporation, reviews of applications (called "supplements") to extend or revise new drug approvals. These evaluations were then compared to in-house analyses. In all five of the supplements reviewed by Mitre, the recommendations were completely congruent with the FDA's own evaluations. Moreover, the time required for the reviews was two to four months, and the cost ranged from \$20,000 to \$70,000 — fast and cheap compared to federal regulators.

Although the FDA has not announced a final decision on changing the policy that permits outside review of medical devices, its elimination would not be a surprise. No matter how efficient or effective it may be, the outsourcing of regulatory functions is wildly unpopular among bureaucrats because it shrinks their budgets and challenges the myth of their uniqueness.

OTHER FDA MISCHIEF

There are other ways in which the FDA has pushed the envelope of its statutory authority in ways that stifle innovation. Although there exists a legal requirement only to show that a new drug is safe and effective, the agency has invented new criteria, including a requirement to demonstrate *superiority* over existing drugs, that it applies arbitrarily. Proving that a test drug is better than existing drugs often is much more difficult and vastly more expensive than just proving that it is safe and effective. If two medicines' efficacies differ only marginally, the clinical trials must be very large in order to show a statistically significant difference between them. Many drugs useful for some patients will founder if this new crite-

tion is widely implemented, reducing competition in the drug market and boosting prices.

Wyeth's chairman and CEO, Robert Essner, described the implications of the requirement to show superiority this way: "If you're the first company to get approved in a certain area and competitors can't get on the market, the FDA is now establishing monopolies. And that's certainly not their mandate." Whatever one thinks of regulation to ensure safety and efficacy, surely we should not have an FDA that aggressively discourages competition.

The FDA has also reversed a sound policy that required prior legal review of warning letters sent to pharmaceutical companies. This will give rise to far more — and more legally dubious — warning letters sent to companies. Another development is an increase in the kinds and amounts of "user fees" that companies must pay just to get the FDA to review their applications. These fees are nothing more than a discriminatory tax that ultimately will be passed on to patients. They are also a shabby attempt to fund government activities "off the books." Congress should scrap the user fees, face up to its responsibilities, appropriate whatever funds it thinks are necessary for the FDA, and then permit the public to judge the results.

AVOIDING TYPE I ERRORS

Sen. Charles E. Grassley (R-IA) once chided drug regulators, "The health and safety of the public must be the FDA's first and only concern." He is right, but particularly when governmental pre-marketing approval of a product is required, greater health and safety are not synonymous with more stringent regulation. In fact, net benefit to patients often suffers because of an obscure regulatory phenomenon — the asymmetry of outcomes from Type I and Type II errors.

A regulator can err by permitting something bad to happen (approving a harmful product, a Type I error) or by preventing something good from becoming available (not approving a beneficial product, a Type II error). The two types of error are opposing sides of the same testing coin — too-assiduous reduction of the incidence of Type I errors typically results in an increase in the incidence of Type II errors.

Both outcomes are bad for the public, but the consequences for the regulator are very different. Type I errors are highly visible, causing the regulators to be attacked by the media and patient groups and to be investigated by Congress, but Type II errors are usually nonevents and elicit little attention, let alone outrage.

The FDA's approval process for new drugs has long struggled with this Type I/Type II dichotomy. Consider, for example, the FDA's approval in 1976 of the swine flu vaccine. That approval is generally perceived to have been a Type I error because, although the vaccine was effective at preventing influenza, it would manifest a major side effect that was unknown at the time of approval — 532 cases of paralysis, including 32 deaths, from Guillain-Barré syndrome.

The mistaken approval of such a product is highly visible and has immediate consequences: the media pounces, the public denounces, and Congress pronounces. The developers

of the product and the regulators who allowed it to be marketed are excoriated and punished in such modern-day pillories as congressional hearings, television newsmagazines, and newspaper editorials. Because a regulatory official's career might be damaged irreparably by the good-faith but mistaken approval of a high-profile product, decisions are often made defensively — in other words, to avoid Type I errors at any cost.

Type II errors in the form of excessive governmental requirements and unreasonable decisions can delay commercialization of a new product, lessen competition to produce it, and inflate its ultimate price. The detrimental effects of FDA delays in approving certain new drugs already approved in other industrialized countries are well-documented. These include the greater than three-year delay in the approval of misoprostol, a drug for the treatment of gastric bleeding, a delay that is estimated to have cost between 8,000 and 15,000 lives per year; and the lag in the approval of streptokinase for the treatment of occluded coronary arteries, which may have caused the loss of more than 10,000 lives per year. Although they can profoundly compromise public health, Type II errors caused by a regulator's bad judgment, timidity, or anxiety seldom gain public attention. Often only the employees of the company that makes the product and a few stock market analysts and investors are likely to be aware of them.

Likewise, if a regulator's mistake precipitates a corporate decision to abandon a product, the cause and effect are seldom connected in the public mind. The companies themselves are loath to complain publicly about FDA misjudgments because the agency wields so much discretionary control over their ability to test and market products. As a consequence, there may be little direct evidence or data to document the lost societal benefits or the culpability of regulatory officials. Former FDA commissioner Alexander Schmidt aptly summarized the regulator's conundrum:

In all our FDA history, we are unable to find a single instance where a Congressional committee investigated the failure of FDA to approve a new drug. But the times when hearings have been held to criticize our approval of a new drug have been so frequent that we have not been able to count them. The message to FDA staff could not be clearer.

As a result, regulators introduce highly risk-averse policies and make decisions defensively — avoiding approvals of potentially harmful products at any cost — and tending to delay or reject new products of all sorts, from fat substitutes to vaccines and painkillers. If a regulator does not understand or is vaguely uneasy about a new product or technology, his instinct is to delay or interdict. That is bad for public health and for consumers' freedom to choose.

What is the remedy for the FDA miasma? For a start, it needs a new ethic, one that better balances the dangers of risk aversion against the benefits of timely approvals. And for that, there will need to be new, more courageous, and intelligent leadership, and more enlightened congressional oversight. I'm not holding my breath. **R**