



## The FDA Amendments Act of 2007 — Assessing Its Effects a Decade Later

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Prescription-drug policy in the United States has developed through a process of punctuated evolution, often driven by crises. Progressive-era concern about “patent medicines” that contained

primarily alcohol or opium led to mandatory labeling under the 1906 Pure Food and Drug Act. The deaths of more than 100 patients from a toxic formulation of sulfanilamide in 1937 resulted in a requirement that manufacturers demonstrate that their products are not lethal. More than two decades later, the thalidomide disaster helped pave the way for 1962 legislation mandating proof of efficacy before a drug could be marketed.

In the early 2000s, the crisis and reform centered around rofecoxib (Vioxx), which became an important trigger for changes in how the Food and Drug Administration (FDA) collects, analyzes, and acts on evidence of drug risks. After rofecoxib entered the market in 1999, several epidemiologic

studies and a large, randomized trial provided disturbing evidence that it increased the risk of cardiovascular events, a concern that could be traced back to earlier clinical trials and laboratory research. The manufacturer dismissed such worries until a large, randomized, placebo-controlled trial, which was stopped early in September 2004, showed that rofecoxib increased the incidence of myocardial infarction and stroke from 0.78 events per 100 patient-years to 1.5 events per 100 patient-years.

By 2006, the public, the scientific community, and Congress were demanding to know how one of the country’s best-selling drugs could carry such important risks without the FDA’s being aware of their magnitude and im-

portance. The agency had long relied on spontaneous, individual case reports of possible adverse reactions as its main source of postapproval surveillance information — a notoriously limited way of identifying problems and quantifying their incidence and severity. It possessed little formal power to compel a manufacturer to perform postapproval studies if safety concerns emerged. Meanwhile, during the prior two decades, several research groups had been using large data sets with information on medication use and clinical events derived from Medicaid, Medicare, and commercial health insurers to study drug effects and utilization. It took the rofecoxib debacle to convince Congress that the FDA should use a similar approach and that it needed more authority to actively manage the evaluation, labeling, and use of approved drug products.

Disturbing accounts had also surfaced in the early 2000s about limited access to the clinical trial

data that formed the basis of FDA approval decisions. For both approved and unapproved drugs, such data were considered proprietary information owned by the manufacturers that sponsored the trials. Negative studies, or those that revealed important side effects, were sometimes difficult to access or were buried altogether, whereas manufacturers widely disseminated trial data more consistent with their marketing messages. Several cases of suppressed studies that had identified risks associated with antidepressant use in children drew particular attention to this issue and contributed to a growing sentiment that the public didn't have adequate access to data about the effects of medications.

Responding to these concerns in the post-Vioxx era, Congress used the 2007 renewal of FDA user-fee legislation to make seminal reforms in the management of data on drug effects. The resulting FDA Amendments Act (FDAAA) instructed the FDA to build a population-based surveillance system to harness the enormous reservoir of data on medication use and clinical events generated automatically during routine electronic recording of filled prescriptions and virtually all other medical encounters. The FDAAA also increased the FDA's power to require manufacturers to conduct postapproval studies, such as by giving it authority to impose monetary penalties for noncompliance. The Act further required that information on the design of all clinical trials be recorded in a public database, ClinicalTrials.gov, soon after a trial's inception, and it set in motion rulemaking to require that summary results also be included in the database within 12 months after the trial's primary comple-

tion date. The law also mandated the implementation of risk evaluation and mitigation strategies (REMS) which can require physician certification, mandatory risk communications, or laboratory testing when specific high-risk medications are used.

These provisions have now been in place for more than a decade, offering an opportunity to assess their effects. The Sentinel system, built and managed by a consortium of academic groups and commercial insurers with FDA oversight, now routinely and systematically assembles anonymized data on filled prescriptions and clinical outcomes for about 67 million Americans. Observational studies that use Sentinel data can assess drug effects in large populations of typical patients receiving care in routine settings, rather than relying on the smaller, highly selected groups of volunteers treated in randomized trials. Large-scale studies of the real-world benefits and risks of anticoagulants illustrate the strengths<sup>1</sup> and challenges<sup>2</sup> of this approach.

The careful curation and organization of data by the Sentinel system and its partners has enabled rigorous postapproval pharmacoepidemiologic research leading to safety communications related to risks associated with widely used medications, such as reports on the association between the angiotensin-receptor blocker olmesartan and chronic diarrhea and weight loss. Heightened attention to postapproval studies can also influence the approval process itself. On the one hand, more attention may be paid to safety signals during initial evaluations if there is a greater likelihood that such effects will be documented after approval. On the other hand, the expecta-

tion of robust postmarketing observational studies could provide justification for less careful evaluation before approval.


Despite Sentinel's contributions, challenges persist. The database is not as accessible as many would like, and linking it to primary health care records is an evolving process. Because of federal restrictions, ascertainment of death is incomplete for many participants. The concept of a system using large amounts of utilization-based health care information was a useful (but not revolutionary) advance in 2007, but continuing developments in the commodification and sale of such data by insurers, the increasing power and decreasing cost of the technology needed to perform these analyses, and methodologic advances in pharmacoepidemiology mean that researchers now have other ways of conducting such studies. In addition, any data set that relies on information from commercial insurers is plagued by the problem that in the United States, many patients frequently change their insurance plan, making studies of medium- and long-term outcomes more difficult — a problem that is not likely to improve.

The FDAAA's provisions related to other postapproval studies have had important effects. Between 2008 and 2014, the FDA mandated 657 studies under the law.<sup>3</sup> However, reports of delayed and incomplete studies continue.<sup>4</sup>

Requirements concerning the availability and transparency of clinical trial data have transformed access to such data. Although several major journals had previously required sponsors to pre-register planned clinical studies at ClinicalTrials.gov, compliance was limited before the FDAAA made such registration compulso-

ry. There is still room for improvement in the speed and completeness of reporting of results, but the legislation and subsequent rule-making have made ClinicalTrials.gov an increasingly useful resource<sup>5</sup> and have limited the ability of sponsors to suppress negative studies or data on adverse effects of approved drugs.

Finally, the FDA has made use of its authority to require REMS to try to mitigate the risks associated with the use of several drugs. Whereas some of these programs have helped promote safer prescribing, others have been less beneficial. For example, REMS programs covering the use of extended-release and long-acting opioids often focus on how to use these products more than on how to avoid prescribing them, and company-run REMS for other opioids appear to have expanded rather than

 An audio interview with Dr. Avorn is available at [NEJM.org](https://www.nejm.org)

contained their use. REMS programs themselves have also been patented by brand-name drug makers in order to limit the entry of generic products into the marketplace — an outcome that could hardly have been predicted when the FDAAA was drafted.

With more than a decade of experience accumulated, it is clear that the FDAAA introduced important improvements in the FDA's capacity to track medication effects and mitigate risk. These features will also provide a means of assessing the effects of more recent efforts to accelerate drug approval and employ a wider range of evidence to demonstrate efficacy — part of the routine ebb of regulation once a crisis has faded. The FDAAA will continue to serve as an important reminder of the lasting power that health-related legislation can have when enacted and enforced intelligently.

Disclosure forms provided by the authors are available at [NEJM.org](https://www.nejm.org).

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DOI: 10.1056/NEJMp1803910

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## Adolescents' Use of "Pod Mod" E-Cigarettes — Urgent Concerns

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Adolescents' use of electronic cigarettes initially took the public health community by surprise. In 2011, less than 2% of U.S. high school students reported having used e-cigarettes in the previous month. But by 2015, the percentage had jumped to 16%. The following year, the U.S. Surgeon General issued a report concluding that e-cigarette use among young people was "a public health concern." Ensuing public education campaigns and policies helped bring the prevalence of past-month e-cigarette use among U.S. high school students down to 11% in 2016.<sup>1</sup>

A recent evolution in technology and marketing may threaten this progress. A new product class called "pod mods" — small, rechargeable devices that aerosolize liquid solutions containing nicotine, flavoring, and other contents encapsulated in cartridges (see graphic) — appears to be gaining traction. Media stories about Juul, a popular pod mod brand, highlight anecdotal reports from students, parents, teachers, and school superintendents indicating that use of these products is rampant among young people. According to Nielsen data, as of January 27, 2018, Juul had cap-

tured 49.6% of the e-cigarette market.<sup>2</sup> There is reason to be concerned that adolescents' use of pod mods is not a passing trend and could bring a host of adverse health consequences to the current generation of adolescents and young adults.

Pod mods may deliver high levels of nicotine with few of the deterrents that are inherent in other tobacco products. Traditional e-cigarette products use solutions with free-base nicotine formulations in which stronger nicotine concentrations can cause aversive user experiences. Juul and other pod mods use protonated