



## The FDA and the Case of Ketek

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Three years ago, the Food and Drug Administration (FDA) approved the drug Ketek (telithromycin), lauding it as the first of a new class of antimicrobial agents that circumvent antibiotic

resistance. Since then, Ketek has been linked to dozens of cases of severe liver injury, been the subject of a series of increasingly urgent safety warnings, and sparked two Congressional investigations of the FDA's acceptance of fraudulent safety data and inappropriate trial methods when it reviewed the drug for approval. As a former FDA physician who was involved in the Ketek review, I believe there are lessons to be learned from an examination of the events surrounding the approval of this product.

Ketek is a ketolide antibiotic manufactured by Sanofi-Aventis and proposed for use in community-acquired respiratory tract in-

fections. It was reviewed by the FDA three times (see timeline). During the first round, reviewers identified substantial safety concerns, including multiple potential drug interactions, unique effects on visual acuity, and an apparent association with hepatocellular hepatitis, with pathological characteristics resembling those caused by drugs that have been withdrawn from the market because of hepatotoxicity. A federal advisory committee asked Sanofi-Aventis to obtain additional safety data by conducting a study involving patients who were likely to receive Ketek if the drug were approved.

In the second review, the FDA examined the results of such a

study. Known as study 3014, it was an unblinded, randomized, controlled trial comparing the incidence rates of hepatic, cardiac, and visual adverse events in patients receiving Ketek and those receiving amoxicillin-clavulanate. Sanofi-Aventis recruited more than 1800 physicians to conduct the study, many of them new to clinical investigation, and paid them as much as \$400 per patient enrolled, primarily to cover the costs of recruiting and gathering research data; more than 24,000 subjects were enrolled. The study was completed in 5 months and purported to show that Ketek was as safe as the other treatment.

A routine FDA inspection of the practices of the physician who enrolled the most patients — more than 400 — uncovered fraud, including complete fabrication of patient enrollment. The inspector notified FDA criminal investiga-

tors, and the physician is currently serving a 57-month sentence in federal prison for her actions. Inspections of nine other sites enrolling high numbers of patients revealed serious violations of trial conduct, raising substantial concerns about the overall integrity of the study. In the end, 4 of the 10 inspected sites were referred for criminal investigation.

Despite these discoveries, FDA managers presented study 3014 to the advisory committee in January 2003 without mentioning the issues of data integrity.<sup>1</sup> The managers have stated that they were legally barred from disclosing the problems to the committee because there was an open criminal investigation, but they have not explained why the data were presented at all, in view of the evidence of the study's lack of integrity. Unaware of the integrity problems, the committee voted 11 to 1 to recommend approval of Ketek.

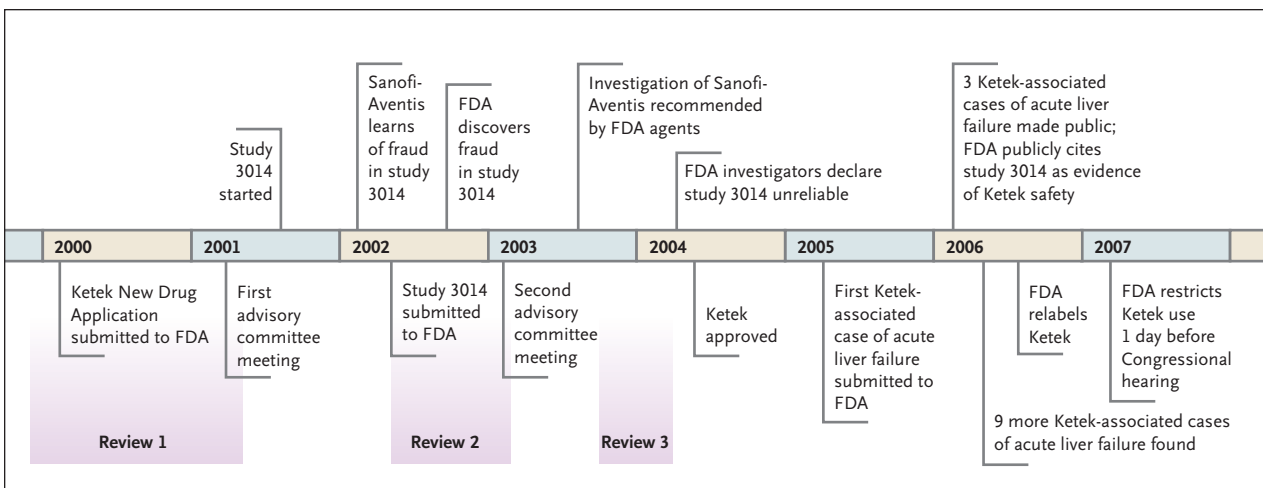
The undisclosed problems with study 3014 led to a third review, during which FDA managers proposed using foreign postmarketing reports on Ketek as evidence of the product's safety, despite the

unreliability of such data.<sup>2</sup> Although drug sponsors are required to submit such reports as part of an application, it is extremely unusual to use these data to address critical preapproval safety issues in place of a controlled study. The postmarketing data submitted by Sanofi-Aventis were reviewed by the FDA without any verification of their accuracy or completeness, even though 3 months before the third review, FDA criminal investigators recommended examining whether Sanofi-Aventis had been involved in systematic fraud in connection with Ketek. The FDA never conducted the recommended investigation or reviewed study 3014-related records showing that Sanofi-Aventis was aware of potential fraud in the study when it submitted the results to the FDA. The failure to look into or respond to concerns about integrity represented a marked deviation from FDA policies.

Against this backdrop of concerns about both safety and fraud, critical questions also arose about the efficacy of Ketek, which had been examined only in noninferiority trials. Such trials are not designed to demonstrate directly

a new intervention's superiority to an active control or a placebo but instead involve the selection of a maximum margin by which the new intervention may be less effective than older interventions but still be considered better than placebo.<sup>3</sup> Throughout the 1990s, noninferiority trials had been standard procedure in the development of antimicrobial agents for the outpatient treatment of self-resolving respiratory tract infections. But by 2004, FDA workshops and advisory committee meetings on this topic had concluded that the use of noninferiority trials in this setting was not justifiable, since there is no evidence of a substantial treatment effect of antimicrobial drugs in self-resolving respiratory tract infections such as acute bacterial sinusitis and acute exacerbation of chronic bronchitis — the diseases for which clinicians most frequently prescribe antimicrobials, for which the market is largest, and for which treatment with Ketek was proposed.

Nevertheless, the FDA approved Ketek entirely on the basis of noninferiority trials. The reason given for the agency's continued acceptance of such trials in the study of



Ketek Timeline.

antibiotics for self-resolving respiratory tract infections was the need to stand by prior agreements with industry sponsors regarding adequate trial designs — the Ketek trials, after all, had been designed and largely conducted before the adequacy of noninferiority trials had been called into question. Once it had been established that such trials could not demonstrate efficacy, however, it might reasonably have been argued that the welfare of prospective patients ought to outweigh any promise to manufacturers. Yet the FDA accepted the trials without discussion of either the patients who might be exposed to a drug that had serious toxic effects — and for which there was no evidence of effectiveness — or the failure of the trials to meet the FDA's own standards at the time of approval.

The review of Ketek was thus marked by pronounced departures from accepted review practices. In addition to the use of fraudulent data, the substitution of uncontrolled postmarket safety reports for controlled clinical trial data, and the acceptance of trials that could not show efficacy, there was also overt internal pressure brought to bear on FDA reviewers to alter their conclusions.

When the FDA approved Ketek on April 1, 2004, the approving officials stated in a memorandum that it was “difficult” to rely on study 3014 for approval<sup>4</sup> but revealed neither the fact that they had known for more than a year about serious problems that compromised the study nor the conclusion by FDA investigators that fraud and a failure of monitoring by Sanofi-Aventis made the study unusable. In this memo, the foreign postmarketing data were put

forward as an acceptable substitute for an adequate and well-controlled trial, without any discussion of the lack of precedent for this approach or the unreliability of such data. Nor did the officials discuss the problems involved with relying on noninferiority trials for treatments of self-resolving infections, the conclusions of previous FDA meetings on this issue, or the applicable FDA standards that had been violated.

Sanofi-Aventis declared in advertisements that Ketek had the most successful launch of any antibiotic in history. In February 2005, 7 months after the drug was introduced to the U.S. market, the first death from Ketek-associated liver failure — in a patient treated for a mild respiratory tract infection — was reported to the FDA. The only formal response was an internal safety review written months later that devoted a few paragraphs to the event.

In January 2006, FDA management learned of the impending electronic report of a cluster of three cases of Ketek-associated acute liver failure at a single medical center, one of them the fatal case that had been reported almost a year earlier.<sup>5</sup> An emergency meeting of FDA senior managers resulted in a public announcement that the FDA regarded Ketek as safe; this announcement cited study 3014 as part of the evidence the FDA had relied on in approving the drug. References to this fraudulent study soon started to creep into the biomedical literature.

In February 2006, I and other reviewers alerted FDA senior management to the irregularities in the Ketek case. FDA management took no substantive actions. In an

internal e-mail, one senior manager, though aware of the fraud in study 3014, defended the agency's citation of it, stating that the review division responsible for Ketek had used it. (Three days after a Congressional hearing on Ketek, in February 2007, the FDA finally removed any mention of study 3014 from its Web site.)

In the face of Congressional subpoenas and unfavorable publicity, reviewers at the FDA were warned at a June 2006 meeting by Andrew von Eschenbach, then the acting FDA commissioner, not to discuss Ketek outside the agency. By this time, 23 cases of acute severe liver injury and 12 cases of acute liver failure, 4 of them fatal, had been linked to Ketek. By the end of 2006, Ketek had been implicated in 53 cases of hepatotoxic effects. The FDA did not relabel Ketek to indicate its possible severe hepatotoxicity until 16 months after the first liver-failure cases became public. The withdrawal of approval for two indications, acute bacterial sinusitis and acute exacerbation of chronic bronchitis, for which Ketek's efficacy had never been demonstrated, did not occur until February 12, 2007 — only a day before the Congressional hearing on Ketek.

To date, the agency has not addressed the actions taken by FDA senior managers in dealing with Ketek, but the hearings recently convened by Congress suggest that it is ready to do so, as part of its efforts to resolve broader problems at the agency. If the case of Ketek leads to important reforms, then the drug may have done some good after all.

An interview with Dr. Ross can be heard at [www.nejm.org](http://www.nejm.org). A letter to the editor from

Soreth and colleagues at the FDA appears on page 1675.

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1. Letter from Senator Charles Grassley to FDA Commissioner Andrew von Eschen-

bach, December 13, 2006. (Accessed March 29, 2007, at <http://finance.senate.gov/press/Gpress/2005/prg121306a.pdf>.)

2. Graham DJ. Telithromycin and acute liver failure. *N Engl J Med* 2006;355:2260-1.

3. Kaul S, Diamond GA. Good enough: a primer on the analysis and interpretation of noninferiority trials. *Ann Intern Med* 2006;145:62-9.

4. Food and Drug Administration, Center for Drug Evaluation and Research. Office/di-

vision memorandum for NDA 21-144 Ketek™ (telithromycin). April 1, 2004. (Accessed March 29, 2007, at [http://www.fda.gov/cder/foi/nda/2004/21-144\\_Ketek\\_Admindocs\\_P1.pdf](http://www.fda.gov/cder/foi/nda/2004/21-144_Ketek_Admindocs_P1.pdf).)

5. Clay KD, Hanson JS, Pope SD, Rissmiller RW, Purdum PP III, Banks PM. Brief communication: severe hepatotoxicity of telithromycin: three case reports and literature review. *Ann Intern Med* 2006;144:415-20.

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## Approving the Vagus-Nerve Stimulator for Depression

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The vagus-nerve stimulator (VNS), a device that is implanted by a neurosurgeon and sends intermittent electrical pulses to the brain, has been marketed in the United States since 1997 as an adjunctive therapy for the control of epilepsy. Debate is ongoing, however, over the use of the device in patients with refractory depression. Though the key clinical questions (Does it work? Is it safe?) seem straightforward, answering them is proving rather complicated. The Food and Drug Administration (FDA) approved the use of the VNS for depression in 2005, but in February 2007, the Centers for Medicare and Medicaid Services issued its preliminary decision not to cover it, citing a lack of scientific evidence of its efficacy, and Blue Cross–Blue Shield had previously turned it down for similar reasons, though both insurers cover its use for epilepsy.

The VNS consists of a round, battery-powered generator about the size of a cardiac pacemaker that is implanted in the chest wall and attached to wires threaded along the vagus nerve in the carotid sheath (see diagram). After surgery, doctors program the gen-

erator to pulse the nerve for 30 seconds once every 5 minutes. The FDA approved the VNS for the treatment of epilepsy after two clinical trials, conducted with patients acting as their own controls, showed that it reduced the rate of seizures by about 25% among patients with refractory epilepsy when used as an adjunct to anti-convulsant drugs. There were frequent side effects, due to the effects of the VNS on the laryngeal nerve — including hoarseness, coughing, dyspnea, and rarely, vocal cord paralysis or infection. The VNS was assessed as safe and effective for patients for whom medication alone had failed, and major insurers accepted its high price — about \$25,000 for the device and the surgery to implant it.

But the indication of clinical depression was added to its label on the basis of less compelling data. In an initial open-label study, 18 of 59 patients with depression had a response to 12 weeks of VNS therapy plus medication. The patients in the trial had been depressed for a median of 6.6 years, and they had received treatment with antidepressants at least twice, and in some cases, many times.

The manufacturer of the VNS, Houston-based Cyberonics, and psychiatrists who were using the VNS in patients with depression called the condition “treatment-resistant depression” and referred to it as “TRD” — as if it were a well-established diagnosis, though it does not appear in the *Diagnostic and Statistical Manual of Mental Disorders* and the notion of a severe, unresponsive form of depression is not universally accepted in the psychiatric literature. Other psychiatrists believe, instead, that depression is an episodic illness for some persons and a chronic condition for others.<sup>1</sup>

A few of the investigators involved in the open-label study, including A. John Rush of the University of Texas Southwestern Medical Center and Mark George of the Medical University of South Carolina, applied to the National Institute of Mental Health for funding for a randomized, controlled, double-blind trial of VNS in depression. Peer reviewers gave the proposal a relatively high rating for scientific merit, but the company withdrew its pledge to supply the devices, so the independent trial could not be pursued. Cyberonics opted to fund