

12-31-2014

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## Recommended Citation

Keith, Ross, "Sending Drugs into the Fast Lane" (2014). *CUNY Academic Works*.  
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## Sending Drugs into the Fast Lane

The FDA is approving drugs faster than ever before but at what cost?

By Ross Keith

Word Count: 2819

When Dr. Aaron Tejani read about the experiment, he knew something was wrong.

It was a scientific test of a revolutionary new drug called Pradaxa, a pill for the most common type of irregular heart rhythm. The Food and Drug Administration was hurrying to get the drug onto the market and had decided to consider approval after just one big study, instead of the usual two.

Tejani, a pharmacist at the Therapeutics Initiative, a drug watchdog group in Vancouver, Canada, still stressed the need for proof. "If we only have one trial," he said. "It'd better be bloody good."

It wasn't. Problems with the trial quickly became clear. But they turned out to be just a hiccup in pharmaceutical company Boehringer Ingelheim's big plans. Errors that led experts like Tejani to doubt the drug's approval were brushed aside and despite some initial hesitation, the FDA eventually approved the drug. Months later, however, the agency was flooded with reports of deaths and uncontrollable bleeding. The shortcomings of the study would eventually lead to an FDA investigation, a multi-million dollar lawsuit settled earlier this year and a serious question: Is the FDA approving drugs too hastily?

Speedy approvals have become increasingly the norm at the FDA, a trend that began in 1992 with the passage of the Prescription Drug User Fee Act. The law has been renewed five times and had a significant impact on speed. Over the past 20 years, the approval process has shrunk, on average, from three years to ten months. The expedited process that was intended to get life saving medicines to patients more quickly is now routinely applied including drugs for weight loss and acne. Nearly 600 drugs have received some form of expedited approval process since 1992, an increase of over 200 percent since 1975. In 2011, over half of all new drugs approved went through some form of expedited review.

As speed has risen, the number of safety issues has as well. Some notoriously harmful drugs, such as Vioxx and Avandia, that were pulled from the market because of dangerous side effects, were fast-tracked. Some doctors and industry analysts question whether the agency's laissez faire approach is essentially moving the testing phase of drugs from the laboratory to the medicine cabinet. Pradaxa is just a recent example of what experts say can happen when safety is sacrificed for speed.

"Drugs are coming to the market, and then dangerous safety concerns are being raised only after thousands, even millions of people had been exposed," said Dr. Steffie Woolhandler, an

expert in drug policy at the City University of New York's School of Public Health. "Literally with patients being guinea pigs," she said.

The FDA did not return requests for comment in time for this story.

### **A policy is born**

Getting drugs on the market quickly was a well intentioned policy. The FDA expedited its process after it faced criticism during the peak of the AIDS crisis.

On October 11, 1988, ACT Up, an international AIDS advocacy group deeply frustrated with the agency shut down the FDA's Maryland headquarters. Badly needed new drugs and treatments were spending years stalled out in the approval process. The protest made the human cost of waiting visible to the country and to the agency. "Hey, Hey, FDA. How many people did you kill today!" they chanted. Archival footage and photos show demonstrators waving pickets signs of bloody handprints in the air and laying on the ground under tombstones.

Change came three years later the major pharmaceutical companies and policymakers reached an agreement on how to change the approval process.

Pressures from the public and politicians prompted a change in the attitude of the agency's senior staff. The pharmaceutical industry was won over after research found that paying the FDA to expedite drug approvals could be cheaper than waiting for the drug to be approved. In response, the FDA promised Congress that with the extra money it could review all new drugs within a year. The Prescription Drug User Fee Act was signed into law November 2, 1992.

The money came with several conditions to help protect the agency's integrity. It could only supplement the agency's budget and payment could never guarantee approval.

"Who wins by the passage of this bill?" asked Congressman John D. Dingell as the House prepared to vote, according to Congressional transcripts. "The American consumer and thousands of patients in dire need of treatment."

Today fees from the industry make up almost 40 percent of the agency's drug evaluation budget. The law has been renewed five times, the latest in 2012. While getting a new drug onto the market remains a lengthy and complex process, the FDA has paved over some of the industry's biggest speedbumps.

The act also established the first two expedited programs, the start of the fast track to approval. The agency has since expanding it to five, allowing any company to enroll in one or more of the programs. If the pharmaceutical company can prove that a drug would treat an

unmet medical need or could be a significant improvement over existing drugs, they can pay for speedy approval.

An inside look at Pradaxa's trip through the approval process exposes the risks that may have come from the focus on speed and the willingness to take risks on new drugs.

### **“Was the RE-LY trial reliable?”**

Blockbuster drugs like Pradaxa don't come along very often. Back in 2009 Boehringer Ingelheim, or BI, could be sure they had a moneymaker. An anticoagulant, it was one of the first drugs of its kind to be released in 50 years. It could help prevent strokes in patients with atrial fibrillation, a type of arrhythmia that affects 34 million people worldwide, according to the World Health Organization. The commonly used treatment for heartbeat irregularities, warfarin, was overdue for replacement. The drug could only be administered by needle, came with strict dietary restrictions and required regular blood testing to make sure the right amount was given. Pradaxa was a simple solution; just take two pills. BI was not the only company trying—eight other major pharmaceutical companies were racing to get their own treatment on the market first. But thanks to the RE-LY trial, Pradaxa was on the fast-track to FDA approval.

Boehringer Ingelheim paid an undisclosed fee to enroll Pradaxa in the Priority Review program, one of the FDA's accelerated approval programs which guarantees that the FDA will decide on a drug in six months. The agency also agreed that BI could submit a rolling application and would only require only one clinical study, the RE-LY trial.

The RE-LY trial took place over six years at seven different testing sites from Florida to Athens. The trial involved around 18000 people. Roughly 12000 of them took Pradaxa. Another 6000 took warfarin. The study showed what BI hoped it would: That Pradaxa just as well as warfarin. At the end of 2009, the study's results were published in the prestigious New England Journal of Medicine and sent to the FDA for approval.

Experts, already worried with how fast the agency was pushing the drug through the pipeline, grew increasingly concerned when problems starting surfacing.

Investigators from the FDA's Division of Scientific Investigations, a branch of the agency that inspects scientific drug testing sites, found problems at five out of BI's seven testing sites in 2007. At one location the mistakes made were so bad that the FDA staff recommended the data shouldn't be used at all. They allowed the researchers to go forward with the results from the other six locations.

When the FDA received the study, they saw mistakes in the numbers without doing any sophisticated analysis—numbers were plainly put into the wrong columns and recorded improperly. That was too much. They refused to approve Pradaxa.

“We recognize that that there may be occasional inaccuracies in a large trial database,” [wrote](#) Alison Blaus, a project manager at the FDA in a letter to BI. “However, the frequency of errors in the data sets impedes our ability to perform an adequate review, and undermines our confidence in your data.”

But two months later, after a closed-door meeting with BI, it reversed its decision without explanation. The FDA agreed to let them re-submit the application. Pradaxa was approved in December 2010.

Meanwhile, thousand of miles away in Vancouver, Dr. Tejani and his colleagues began writing an article outlining his serious concerns with the RE-LY trial.

The doctors from McMaster University, a private college outside of Toronto, who were responsible for overseeing the trial would not share the study data. Luckily the FDA had published some of it in their reviews. Tejani and his co-authors found that instead of recording all side effects patients experienced while taking the drug, the study had only kept track of side effects that they had expected. The FDA, along with Tejani, had also noted the study had only documented side-effects if they occurred six days after patients had taken a dose to match the time the drug stayed in the body.

Serious, even fatal, side effects were left out of the report.

“These arbitrary definitions don’t make any clinical sense,” he said. “It’s a very close minded approach.”

Tejani admits no study is perfect. Every trial has a little bit of bias, some more than others. But one of the most simple tenets of the scientific method is that any study needs to be replicable. He said there are plenty of examples where patients have been hurt by drugs because initial studies were taken at their word.

“So many people have been harmed because we’re in a rush,” he said. “Do we want to keep making the same mistakes again?”

Despite the concern from experts like Tejani, Pradaxa was approved in December 2010. The researchers at McMaster published a correction to their original article in 2010 and BI’s marketing machine began gearing up to sell the new drug.

### **Too much, too quickly?**

In less than a month the FDA started receiving serious reports of side effects including vomiting, chest pains and internal bleeding. Serious bleeding is a well-known risk of anticoagulants like Pradaxa and warfarin, but the numbers were disturbing. In three months

after approval, the FDA received more reports of deaths and serious side effects than any other regularly monitored drug.

In September, 2011, the Institute of Safe Medication Practices, a drug safety organization, published the report of FDA data and two months before the FDA announced it would launch an official safety investigation.

Scientists at the group expressed concern about how quickly the drug had been picked up by doctors and widely prescribed despite its haphazard trip through the approval process. One side effect in particular alarmed the advocates. While taking warfarin was inconvenient, any excess bleeding could be stopped with an antidote. Patients taking Pradaxa weren't so lucky. There were almost no options to stop the bleeding. The safety report questioned whether the FDA had traded one problem for another.

Not long after, patients started coming forward to press legal action against Boehringer Ingelheim and McMaster University the risks of Pradaxa and the integrity of the RE-LY trial. Thomas Moore and Dr. Curt Furdberg of the Institute of Safe Medication Practices published another report on Pradaxa in the Journal of American Medicine. The scientists questioned whether the FDA had let the drug on the market too soon. This led to a broader question on how many drugs deserved to go through the expedited drug approval pathway. Almost half of all drugs approved in 2011 were accelerated through at least one program. Pradaxa got special attention. It had been fast-tracked through three.

"All the skids were greased," said Dr. Sidney Wolfe, a drug safety expert and scientist at Public Citizen, a consumer advocacy group. And Pradaxa isn't even the worst case, according to Wolfe.

"Some could argue that it should be approved," said Wolfe, "There's drugs that nobody could argue should have been approved." Meridia, a diet drug was approved in 1997 even after the FDA's own staff denied the drug. The FDA pulled it from the market more than a decade later, after studies finally showed that it was causing heart attacks.

### **Has the PDUFA affected safety?**

Earlier this year, researchers from Harvard University, Boston University, the City University of New York and Public Citizen analyzed thirty-five years worth of approval and safety data. The team set out to find the impact of the Prescription Drug User Fee Act and published their findings this August in Health Affairs, a medical policy journal.

They examined drugs that had been pulled from the market for safety reasons or given black box warnings, the FDA's gravest warning, and determined as the speed of the drug approval process was accelerating, a greater number of safety concerns was becoming apparent. For every 100 drugs before 1992 there were 21.2 safety problems. After 1992, there were 26.7 for

every 100 drugs. One third of all new drugs eventually had a safety problem recognized by the FDA.

“Certainly there could be other factors that could explain this uptick,” said Dr. Cassie Frank, the study’s lead author. “But we felt there was a lot of data that suggested that part of this reason, a strong part, is that the FDA continues to be reckless with their pre-approval process.”

The data wasn’t easy to find. Frank explains that it required combing through stacks of books and old FDA reports. They were conservative in their estimate. They only included safety recalls initiated by the FDA, even though the vast majority of recalls are voluntary. The authors admit that their data is imperfect but still meaningful.

“At some level there has to be a way to evaluate the safety of drugs.” said Frank “These are the FDA’s most serious safety warnings. They have increased, now the question is why.”

### **In with a bang, out with a whimper**

Patients purchasing Pradaxa in 2013 may have noticed something new on the box. The FDA issued a black box warning for the drug that year, warning patients of extreme to fatal side effects if they stopped taking the drug.

Fast forward to the lawsuit. Earlier this year, over 4,000 patients had joined together in a multidistrict case against Boehringer Ingelheim. The legal battle had been building momentum for years and the first cases were finally scheduled to begin in September.

Anticlimatically, they settled the case out of court for 650 million--without a single patient testifying. In a statement, Boehringer Ingelheim characterized the lawsuit as a consequence of an overeager legal system and said settling now would free them to concentrate on improving patients lives.

During the course of the trial, BI, had been forced to release all communications between corporate staff about the drug and preliminary reports from the RE-LY trial. In March, the documents became the center of an investigation by an editor at the British Medical Journal, Dr. Deborah Cohen. She uncovered evidence that important information had been held back about the drug.

Cohen found the doctors running the RE-LY trial had advised that monitoring blood levels could make patients five times safer. However, BI company official hid the reports from the FDA and regulators in other countries for marketing purposes. The monitoring could have changed the appearance that Pradaxa was easier to manage and hurt sales.

Boehringer Ingelheim dismissed the report, saying that the preliminary reports had no impact on the study's results.

Pradaxa popularity had already diminished said Dr. Blake Charlton, who works at the University of California San Francisco Medical Center and wrote an accompanying article alongside Cohen's investigation. Charlton said that using Pradaxa or one of the other new anticoagulants that are now on the market makes him nervous. In the rush to get the treatments onto the market, no one developed an antidote to reverse the bleeding.

Looking back, Charlton said that the FDA was overenthusiastic about Pradaxa and there was no justification to rush it through the approval process. And it raises bigger questions about the consequences of rushing drugs through the approval process.

"The FDA needs to do some soul searching about the fast track program and how it works in real life," he said.

The story of Pradaxa tells a cautionary tale. It's not the only one of it's kind. Kim Witczak, a patient advocate who operates, [Woodymatters.com](http://Woodymatters.com), lost her husband after he committed suicide, shortly after he started taking Zoloft. Witczak has testified before Congress and the FDA on drug safety.

"When people see a drug on the shelf, they assume it's been through rigorous FDA testing," she said.

By speeding up the drug approval process, the FDA takes a calculated risk when it comes to side effects. But Witczak argues that it's a risk consumers should be aware of. While these negative side effects may affect only a small percentage of patients, it's enough to matter.

"That's somebody's 100 percent." said Witczak.