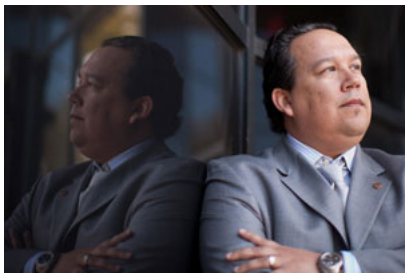
FDA Let Drugs Approved on Fraudulent Research Stay on the Market

by Rob Garver and Charles Seife, Special to ProPublica, April 15, 2013, 9:17 a.m.

On the morning of May 3, 2010, three agents of the Food and Drug Administration descended upon the Houston office of Cetero Research, a firm that conducted research for drug companies worldwide.



Retired FDA investigator Patrick Stone (Katie Hayes Luke for ProPublica)

Lead agent Patrick Stone, now retired from the FDA, had visited the Houston lab many times over the previous decade for routine inspections. This time was different. His team was there to investigate a former employee's allegation that the company had tampered with records and manipulated test data.

When Stone explained the gravity of the inquiry to Chinna Pamidi, the testing facility's president, the Cetero executive made a brief phone call. Moments later, employees rolled in eight flatbed carts, each double-stacked with file boxes. The documents represented five years of data from some 1,400 drug trials.

Pamidi bluntly acknowledged that much of the lab's work was fraudulent, Stone said. "You got us," Stone recalled him saying.

Based partly on records in the file boxes, the FDA eventually concluded that the lab's violations were so "egregious" and pervasive that studies conducted there between April 2005 and August 2009 might be worthless.

The health threat was potentially serious: About 100 drugs, including sophisticated chemotherapy compounds and addictive prescription painkillers, had been approved for sale in the United States at least in part on the strength of Cetero Houston's tainted tests. The vast majority, 81, were generic versions of brand-name drugs on which Cetero scientists had often run critical tests to determine whether the copies did, in fact, act the same in the body as the originals. For example, one of these generic drugs was ibuprofen, sold as gelatin capsules by one of the nation's largest grocery-store chains for months before the FDA received assurance they were safe.

The rest were new medications that required so much research to win approval that the FDA says Cetero's tests were rarely crucial.

Stone said he expected the FDA to move swiftly to compel new testing and to publicly warn patients and doctors.

Instead, the agency decided to handle the matter quietly, evaluating the medicines with virtually no public disclosure of what it had discovered. It pulled none of the drugs from the market, even temporarily, letting consumers take the ibuprofen and other medicines it no longer knew for sure were safe and effective. To this day, some drugs remain on the market despite the FDA having no additional scientific evidence to back up the safety and efficacy of these drugs.

By contrast, the FDA's transatlantic counterpart, the European Medicines Agency, has pulled seven Cetero-tested medicines from the market.

The FDA also has moved slowly to shore up the science behind the drugs. Twice the FDA announced it was requiring drug makers to repeat, reanalyze or audit many of Cetero's tests, and to submit their findings to the agency. Both times the agency set deadlines, yet it has allowed some companies to blow by them.

Today, six months after the last of those deadlines expired and almost three years after Cetero's misconduct was discovered, the FDA has received the required submissions for just 53 drugs. The agency says most companies met the deadlines but acknowledged that "a few have not yet submitted new studies [1]."

Other companies, it said, have not submitted new research because they removed their drugs from the market altogether.

Key Points

- In 2011, the FDA announced years' worth of studies from a major drug research lab were potentially worthless.
- About 100 drugs were on the U.S. market based in part on these tests.
- The FDA let the drugs stay on pharmacy shelves with no new testing (in some cases until now).
- As the FDA investigated and ordered re-tests, its European equivalent pulled seven drugs from the market.
- The FDA says it has no evidence that any of the drugs were unsafe or that any patient has been harmed.
- The FDA has never named the drugs, saying to do so would reveal trade secrets.

For its part, the FDA has finished its review of just 21 of the 53 submissions it has received, raising the possibility that patients are taking medications today that the agency might pull off the market tomorrow.

To this day, the agency refuses to disclose the names of the drugs it is reassessing, on the grounds that doing so would expose "confidential commercial information." ProPublica managed to identify five drugs [2] that used Cetero tests to help win FDA approval.

FDA officials defended the agency's handling of the Cetero case as prudent and scientifically sound, noting that the agency has found no discrepancies between any original drug and its generic copy and no sign that any patients have been harmed.

"It is non-trivial to have to redo all this, to withdraw drugs, to alarm the public and the providers for a large range of drugs," said Janet Woodcock, the director of the FDA's Center for Drug Evaluation and Research. "There are consequences. To repeat the studies requires human experimentation, and that is not totally without risk."

Woodcock added that an agency risk assessment found the potential for harm from drugs tested by Cetero to be "quite low," an assessment she said has been "confirmed" by the fact that no problems have been found in the drugs the agency has finished reviewing.

She declined to release the risk assessment or detail its design. A subsequent statement from the agency described the assessment as "fluid" and "ongoing." The FDA also has not released its 21 completed reviews, which ProPublica has requested.

Some experts say that by withholding so much information in the Cetero case the FDA failed to meet its obligations to the public.

"If there are problems with the scientific studies, as there have been in this case, then the FDA's review of those problems needs to be transparent," said David Kessler, who headed the FDA from 1990 to 1997 and who is now a professor at the University of California at San Francisco. Putting its reviews in public view would let the medical community "understand the basis for the agency's actions," he said. "FDA may be right here, but if it wants public confidence, they should be transparent. Otherwise it's just a black box."

Another former senior FDA official, who spoke on condition of anonymity, also felt the FDA had moved too slowly and secretively. "They're keeping it all in the dark. It's not transparent at all," he said.

By contrast, the European Medicines Agency has provided a public accounting of the science behind all the drugs it has reviewed. Its policy, the EMA said in response to questions, is to make public "all review procedures where the benefit-risk balance of a medicine is under scrutiny."

Woodcock dismissed comparisons to the EMA. "Europe had a smaller handful of drugs," she said, "and they may not have engaged in as extensive negotiation and investigations with the company as we did."

She said the FDA would have disclosed more, including the names of drugs, had it believed there was a risk to public health. "We believe that this did not rise to the level where the public should be notified," she said. "We felt it would result in misunderstanding and inappropriate actions."

In a written response to Kessler's comments, the FDA said, "We've been as transparent as possible given the legal protections surrounding an FDA investigation of this or any type. The issue is not a lack of transparency but rather the difficulty of explaining why the problems we identified at Cetero, which on their face would appear to be highly significant in terms of patient risk, fortunately were not."

Still, the FDA's secrecy has had other ramifications. Some of Cetero's suspect research made its way unchallenged into the peer-reviewed scientific literature on which the medical community relies. In one case, a researcher and a journal editor told ProPublica they had no idea the Cetero tests had been called into doubt.

Cetero, in correspondence with the FDA, conceded misconduct. And in an interview, Cetero's former attorney, Marc Scheineson, acknowledged that chemists at the Houston facility committed fraud but said the problem was limited to six people who had all been fired.

"There is still zero evidence that any of the test results…were wrong, inaccurate, or incorrect," he said. Scheineson called the FDA's actions "overkill" and said they led to the demise of Cetero and its successor company.

In 2012, the company filed for Chapter 11 bankruptcy and emerged with a new name, PRACS Institute. PRACS, in turn, filed for bankruptcy on March 22 of this year. A PRACS spokesperson said the company had closed the Houston facility in October 2012.

Pamidi, the Cetero executive who provided the carts of file boxes, declined to comment.

As for Stone, the former FDA investigator, he said he was disturbed by the agency's decisions.

"They could have done more," he said. "They should have done more."

'We Should Have Been Told'

Cross-checking U.S. and European public records, including regulatory filings, scientific studies and civil lawsuits, ProPublica was able to identify a few of the drugs that are on the U.S. market because of tests performed at Cetero's Houston lab (see chart [2].) There is no evidence that patients have suffered harm from these drugs; the FDA says it has detected no increase in reports of side effects or lack of efficacy among Cetero-tested medications.

To be sure, just because a crucial study is deemed potentially unreliable does not mean that a drug is unsafe or ineffective. What it does mean is that the FDA's scientific basis for approving that drug has been undermined.

The risks are real, academic experts say, particularly for drugs such as blood thinners and anti-seizure medications that must be given at very specific doses. And generic versions of drugs have been known to act differently from name-brand products (see accompanying story [3].)

There is no indication the generic ibuprofen gelatin capsules hurt anyone, but their case shows how the FDA left a drug on the market for months without confirmation that the drug was equivalent to the name brand.

The capsules were manufactured by Banner Pharmacaps and carried by Supervalu, a grocery company that operates or licenses more than 2,400 stores across the United States, including Albertson's, Jewel-Osco, Shop 'n Save, Save-A-Lot, and Shoppers Food & Pharmacy.

Cetero had performed a key analysis [4] to show that the capsules were equivalent to other forms of the drug. Banner, the drug's maker, said the FDA first alerted it to the problems at Cetero in August 2011. The FDA required drug companies to redo many of Cetero's tests, but, a spokesperson for Banner wrote in an email, "We received no directive from FDA to recall or otherwise interrupt manufacture of the product."

Banner said it repeated the tainted Cetero tests at a different research firm, and the FDA said it received the new data in January 2012 — leaving a gap of at least five months when the FDA knew the drug was on the market without a rock-solid scientific basis.

An FDA spokesperson wrote in an email that the agency found the new studies Banner submitted "acceptable" and told Banner it had no further questions.

A spokesperson for Supervalu told ProPublica it purchased the ibuprofen from a supplier, which has assured the grocery company that "there are no issues with the product."

According to U.S. and European records, another one of the drugs approved based on research at Cetero's troubled Houston lab was a chemotherapy drug known as Temodar for Injection.

Temodar was originally approved in 1999 as a capsule to fight an aggressive brain cancer, glioblastoma multiforme. Some patients, however, can't tolerate taking the medication orally, so drug maker Schering-Plough decided to make an intravenous form of the drug.

To get Temodar for Injection approved, the FDA required what it called a "pivotal" test comparing the well-established capsule form of Temodar to the form injected directly into the bloodstream.

Cetero Houston conducted that test, comparing blood samples of patients who received the capsule to samples of those who got the injection to determine if the same amount of the drug was reaching the bloodstream. This test is crucial, particularly in the case of Temodar, where there was a question about the right dosing regimen [5] of the injectable version. If too little drug gets into the blood, the cancer could continue to grow unabated. If too much gets in, the drug's debilitating side effects could be even worse.

Cetero performed the test between September 2006 and October 2007, according to documents [6] from the European Medicines Agency, and FDA records [7] indicate that same test was used to win approval in the U.S.

In 2011, the FDA notified Merck & Co., which had acquired Schering-Plough, about the problems with Cetero's testing. In April 2012, the FDA publicly announced that analyses done by Cetero during the time when it performed the Temodar work would have to be redone. But according to Merck spokesman Ronald Rogers, the FDA has not asked Merck for any additional analyses to replace the questionable study.

The FDA declined to answer specific questions about the Temodar case, saying to do so would reveal confidential commercial information. But Woodcock said that in some cases, drug manufacturers had submitted alternative test results to the FDA that satisfied the agency that no retesting was necessary for specific drugs.

The FDA never removed Temodar for Injection from the market. The European Medicines Agency also kept the injection form of the drug on the market, but the two agencies handled their decision in sharply different ways.

The EMA has publicly laid out evidence [8] — including studies not performed by Cetero — for why it believes the benefits of the injection drug outweigh its risks. But in the United States, the FDA has kept silent. To this day, Temodar's label [9] — the single most important way the FDA communicates the risks and benefits of medication — still displays data from the dubious Cetero study. (The label of at least one other drug, a powerful pain reliever marketed as Lazanda [10], also still displays questionable Cetero data.)

Woodcock said the agency hadn't required manufacturers to alter their labels because, despite any question about precise numerical precision, the FDA's overall recommendation had not changed.

In a written response to questions, Merck said it "stands behind the data in the TEMODAR (temozolomide) label." The company said it learned about "misconduct at a contract research organization (CRO) facility in Houston" from the FDA and that it cooperated with investigations by the FDA and its European counterpart. It said that Cetero had performed no other studies for Merck.

Even one of the researchers involved in evaluating injectable Temodar didn't know that the FDA had flagged Cetero's analysis as potentially unreliable until contacted by a reporter for this story.

Dr. Max Schwarz, an oncologist and clinical professor at Monash University in Melbourne, Australia, treated some brain-cancer patients with the experimental injectable form of Temodar and others with the capsule formulation. Blood from his patients was sent to Cetero's Houston lab for analysis.

Schwarz said he still has confidence in the injectable form of the drug, but said that he was "taken aback" when a reporter told him that the FDA had raised questions about the analysis. "I think we should have been told," he said.

Suspect research conducted by Cetero Houston was not only used to win FDA approval but was also submitted to peer-reviewed scientific journals. Aided by the FDA's silence, those articles remain in the scientific literature with no indication that they might, in fact, be compromised. For example, based on Cetero's work, an article in the journal Cancer Chemotherapy and Pharmacology purports to show that Temodar for Injection is equivalent to Temodar capsules.

Edward Sausville, co-editor-in-chief of the journal, said in an email that the first he heard that something might be wrong with the Cetero research was when a reporter contacted him for this story. He also said the publisher of the journal would conduct a "review of relevant records pertinent to this case."

'There's Always Something Missing'

During his years of inspecting the Houston lab, the FDA's Stone said he often had the sense that something wasn't right. When he went to other contract research firms and asked for data on a trial, they generally produced an overwhelming amount of paper: records of failed tests, meticulous explanations of how the chemists had made adjustments, and more.

Cetero's records, by contrast, showed very clean, error-free procedures. As Stone and his colleagues dug through the data, though, they often found gaps. When pressed, Cetero officials would often produce additional data — data that ought to have been in the files originally handed over to the FDA.

Stone said, "We should have looked back and said, ‘Wait a minute, there's always something missing from the studies from here. Why?'"

One reason, the FDA would determine, was that Cetero's chemists were taking shortcuts and other actions prohibited by the FDA's Good Laboratory Practice guidelines, which set out such matters as how records must be kept and how tests must be performed.

Stone and his FDA colleagues might never have realized Cetero was engaging in misconduct if a whistleblower hadn't stepped forward.

Cashton J. Briscoe operated a liquid chromatography-tandem mass spectrometry device, or "mass spec," a sensitive machine that measures the concentration of a drug in the blood.

He took blood samples prepared by Cetero chemists and used mass specs to perform "runs" — tests to see how much of a drug is in patients' blood — that must always be performed with control samples. Often those controls show readings that are clearly wrong, and chemists have to abort runs, document the failure, recalibrate the machines, and redo the whole process.

But Cetero paid its Houston chemists based on how many runs they completed in a day. Some chemists doubled or even tripled their income by squeezing in extra tests, according to time sheets entered as evidence in a lawsuit filed in U.S. District Court in Houston by six chemists seeking overtime payments. Briscoe thought several chemists were cutting corners — by using the control-sample readings from one run in other runs, for example.

Attorney Scheineson, who represented Cetero during the FDA's investigation, acknowledged that the Houston lab's compensation system was "crappy" and that a handful of "dishonest" chemists at the Houston facility committed fraud.

In April 2009, Briscoe blew the whistle in a letter to the company written by his lawyer, reporting that "many of the chemists were manipulating and falsifying data." Soon thereafter, Briscoe told the company that he had documented the misconduct. According to Stone and documents reviewed by ProPublica, Briscoe had photographic evidence that mass spec operators had switched the quality control samples between different runs; before-and-after copies of documents with the dates and other material changed; and information about a shadow computer filing system, where data from failed runs could be stored out of sight of FDA inspectors.

On June 5, apparently frustrated with Cetero's response, Briscoe went a step further and called the FDA's Dallas office. He agreed to meet Stone the following Monday, but never showed. Stone called him, as did other FDA officials, but Briscoe had changed his mind and clammed up.

Still, Stone's brief phone conversation with Briscoe reminded the agent of all those suspiciously clean records he had seen at Cetero over the years. "Now that you have a bigger picture," Stone recalled, "you're like, 'Oh, some of this stuff is cooked.'"

Two days after Stone's aborted meeting with Briscoe, Cetero informed the FDA that an employee had made allegations of misconduct and that the company had hired an outside auditor to review five years' worth of data. That led to months of back-and-forth between the agency and Cetero that culminated when Stone and his inspectors arrived in Houston in May 2010.

Two teams of FDA investigators eventually [11] confirmed [12] Briscoe's main allegations and cited the company for falsifying records and other violations of Good Laboratory Practice. The net effect of the misconduct was far-reaching, agency officials wrote in a July 2011 letter [13]:

"The pervasiveness and egregious nature of the violative practices by your firm has led FDA to have significant concerns that the bioequivalence and bioavailability data generated at the Cetero Houston facility from April 1, 2005, to June 15, 2010 ... are unreliable."

Bioequivalence studies measure whether a generic drug acts the same in the body as the name-brand drug; bioavailability studies measure how much drug gets into a patient's system.

The FDA's next step was to try to determine which drugs were implicated — information the agency couldn't glean from its own records.

"We couldn't really tell — because most of the applications we get are in paper — which studies were actually linked to the key studies in an application without asking the application holders," the FDA's Woodcock said. "So we asked the application holders," meaning the drug manufacturers.

In the interim, the FDA continued to investigate processes and procedures at Cetero.

"We put their operations under a microscope," said Woodcock. A team of clinical pharmacologists, statisticians and IT experts conducted a risk analysis of the problems at Cetero, she said, and they "concluded that the risk of a misleading result was very low given how the studies were done, how the data were captured and so forth."

In April 2012, nearly three years after Briscoe first alerted the FDA to problems at Cetero, and nearly two years after Cetero handed over its documentation to inspectors, the FDA entered into a final agreement with the company. Drug makers would need to redo tests conducted at the company's Houston facility between April 1, 2005 and Feb. 28, 2008, if those studies had been part of a drug application submitted to the FDA. If stored blood samples were still usable, they could be reanalyzed. If not, the entire study would need to be repeated, the FDA said. The agency set a deadline of six months.

Cetero tests done between March 1, 2008 and Aug. 31, 2009 would be accepted only if they were accompanied by an independent data integrity audit.

Analyses done after Sept. 1, 2009 would not require retesting. The FDA said that Cetero had issued a written directive on Sept. 1, 2009, ordering one kind of misconduct to stop, which was why it did not require any action on Cetero Houston studies after that date. According to public documents, however, the agency's inspectors "found continued deficiencies [14]" that persisted into December 2010.

In response to questions, the FDA said the problem period "was subsequently narrowed as more information regarding Cetero's practices became available."

A year after concluding its final agreement with Cetero, the FDA's review is still not finished. "Without the process being public it's hard to know, but it seems that this has been going on for too long," said Kessler, the former FDA chief.

"The process has been long," the FDA said, "because of the number of products involved and our wish to be thorough and accurate in both our requests for and our review of the data."

Cetero's attorney Scheineson said the FDA scaled back its requirements because it finally talked with company officials. He noted that Cetero had tried repeatedly to talk with the FDA before the agency issued its strongly worded July 2011 letter, and that more than 1,000 employees have since lost their jobs.

"If you would get an honest assessment from the leaders of the agency," he said, "I think in retrospect they would have argued that this was overkill here and that they should have had input from the company before essentially going public with that death sentence."

"I'm not sure what is meant by 'death sentence,'" an FDA spokesperson wrote in response, "but our first priority was and is patient safety and we proceeded to conduct the investigation toward that objective."

'Should I Be Proud of This?'

The FDA's Stone draws little satisfaction from unraveling the problems at Cetero.

There are thousands of bioequivalence studies done every year, he pointed out, with each study generating thousands of pages of paper records. "Do you really think we're going to look at 100 percent of them? We're going to look at maybe 5 percent if we're lucky," he said. "Sometimes 1 percent."

Still, given how often he and other FDA teams had inspected the Houston lab, he thinks regulators should have spotted Cetero's misconduct sooner.

"In hindsight I look back and I'm like, 'Wow, should I be proud of this?'" he said. "It's cool that I was part of it, but it's crap that we didn't catch it five years ago. How could we let this go so long?"

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