# FDA Keeps Brand-Name Drugs on a Fast Path to Market — Despite Manufacturing Concerns

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After unanimously voting to recommend a miraculous hepatitis C drug for approval in 2013, a panel of experts advising the Food and Drug Administration gushed about what they'd accomplished.

"I voted 'yes' because, quite simply, this is a game changer," National Institutes of Health hepatologist Marc Ghany, MD, said of Sovaldi, Gilead Science's new pill designed to cure most cases of hepatitis C within 12 weeks.

Lawrence Friedman, MD, a professor at Harvard Medical School, called it his "favorite vote" as an FDA reviewer, according to the transcript.

What the panelists didn't know was that the FDA's drug quality inspectors had recommended against approval.

They issued a scathing 15-item disciplinary report after finding multiple violations at Gilead's main U.S. drug testing laboratory, down the road from its headquarters in Foster City, Calif. Their findings criticized aspects of the quality control process from start to finish: Samples were improperly stored and catalogued; failures were not adequately reviewed; and results were vulnerable to tampering that could hide problems.

Gilead Foster City doesn't manufacture drugs. Its job is to test samples from drug batches to ensure the pills don't crumble or contain mold, glass or bacteria, or have too little of an active antiviral ingredient.

Recent news reports have focused public attention on poor quality control and contamination in the manufacturing of cheap generic drugs, particularly those made overseas. But even some of the newest, most expensive brand-name medicines have been plagued by quality and safety concerns during production, a Kaiser Health News analysis shows.

More disturbing, even when FDA inspectors flagged the potential danger and raised red flags internally, those problems were resolved with the agency in secret — without a follow-up inspection — and the drugs were approved for sale.

Erin Fox, who purchases medicines for University of Utah Health hospitals, said she was shocked to hear from KHN about manufacturing problems uncovered by authorities at the facilities that make brand-name products. “Either you’re following the rules or you’re not following the rules,” Fox said. “Maybe it’s just as bad for branded drugs.”

The pressure to get innovative drugs like Sovaldi into use is considerable, both because they offer new treatments for desperate patients and because the medicines are highly profitable.

Against that backdrop, the FDA has repeatedly found a way to approve brand-name drugs despite safety concerns at manufacturing facilities that had prompted inspectors to push to reject those drugs’ approval, an ongoing KHN investigation shows. This happened in 2018 with drugs for cancer, migraines, HIV and a rare disease, and 10 other times in recent years, federal records show. In such cases, how these issues were discussed, negotiated and ultimately resolved is not public record.

For example, inspectors found that facilities making immunotherapies and migraine treatments didn’t follow up when drug products showed evidence of bacteria, glass or other contaminants. At a Chinese plant making the new HIV drug Trogarzo, employees dismissed “black residue” found to be “non-dissolvable metal oxides,” assuming it “did not pose a significant risk,” federal records show.

Without a follow-up inspection to confirm drugmakers corrected the problems inspectors found, these medicines eventually were approved for sale, and at list prices as high as $189,000 a month for an average patient, according to health data firm Connecture. The cancer drug Lutathera was initially rejected over manufacturing problems at three plants but was approved a year later without a fresh inspection and was priced at $57,000 per vial.

John Avellanet, a consultant on FDA compliance, said data integrity problems, like those at Gilead’s lab in Foster City, should have sparked further investigation, because they raise the possibility of “deeper issues.”

Dr. Janet Woodcock, the director of the FDA’s Center for Drug Evaluation and Research, said an inspector’s recommendation to withhold approval can be “dealt with” without a follow-up. Woodcock said the agency can’t comment on specifics, and companies are reluctant to discuss them because the details of the resolution are protected as a corporate trade secret.

“That doesn’t mean that there’s anything wrong with the drug,” Woodcock said.

Dinesh Thakur, a former drug-quality employee turned whistleblower, called the secrecy a “red flag.” A follow-up inspection is critical, he said: “I’ve seen many times paper commitments are made but never followed through.”

What worries Fox is that a faulty drug could get through and nobody would know.

“In general, very few people suspect that their medicine is the problem or their medicine is not working,” Fox said. “Unless you see black shavings or something horrible in the product itself, the drug is almost the last thing that would be suspect.”

The Market Beckons

If the FDA finds problems at preapproval inspections for generics, the agency is likely to deny approval and delay the drug’s launch until the next year’s review cycle, according to industry and agency experts.

In fact, just 12% of generics were approved the first time their sponsors submitted applications from 2015 through 2017.

The calculus appears different for heralded new therapies like Sovaldi. In 2018, 95% of novel drugs — the newest of the new — were approved on the first try, the FDA said.

Woodcock said the agency has “the same standards for all drugs,” but she emphasized that many of the manufacturing issues “are somewhat subjective.”

For new brand-name drugs, she said, the FDA “will work very closely with the company to … bring the manufacturing up to snuff.”

The manufacturer submits written responses and commits to resolve quality concerns, but the details are kept confidential.

An estimated 2.4 million Americans have hepatitis C and, before Sovaldi, treatment came with miserable side effects and a strong chance it wouldn’t work. Sovaldi promised up to a 90% cure rate, though it came with an eye-popping $84,000 price tag for a 12-week course, putting it out of reach for most patients and health care systems.

But corporate pressure to get such therapies into the marketplace is also considerable.

Pharmaceutical firms pay hefty fees for FDA review and lobby the agency to speed products to market. For Gilead, time lost is money.

“If approval of sofosbuvir were delayed, our anticipated revenues and our stock price would be adversely affected,” Gilead wrote in an SEC document filed Oct. 31, 2013, using the generic name for Sovaldi.

Since its debut in 2013, Sovaldi has been widely criticized for its price but recognized as a medical breakthrough. Gilead has never recalled it.

However, hundreds of patients who have taken the drug have voluntarily reported cancer or other complications to the FDA’s “adverse event” reporting database, including concerns that the

treatment doesn't always work. One in 5 Sovaldi patients and health care professionals who reported serious problems to federal regulators said the drug didn't cure the patients' hepatitis C.

"The FDA approved these products after a rigorous inspection process, and we are confident in the quality/compliance of these products," Gilead spokeswoman Sonia Choi said.

Problems at Foster City

Gilead's Foster City facility has been cited for an array of problems over the years. In 2012, FDA inspectors said the facility had failed to properly review how the HIV drugs Truvada and Atripla became contaminated with "blue glass" particles; some of that tainted batch was distributed. The company "made no attempt to recover" the contaminated drugs, according to FDA inspection records.

Gilead had just filed its application for Sovaldi's approval when FDA inspectors arrived at Foster City for an unrelated inspection in April 2013. Inspectors slapped the facility with nine violations in what's called a 483 document and said that the reliability of the site's methods for testing things like purity were unproven and that its records were incomplete and disorganized, according to FDA inspection documents.

As a result, the FDA initially rejected two HIV drugs, Vitekta and Tybost. Gilead had to resubmit those applications, and it would take 18 months before the FDA approved them in late 2014.

On Sept. 19, 2013, FDA officials met to discuss Sovaldi with Woodcock, agency records show. Meeting minutes show inspectors recommended hitting Gilead Foster City with a formal warning letter based on the April inspection. (A warning letter is a disciplinary action from the FDA that typically includes a threat to withhold new approvals or place a foreign facility on import alert and refuse to accept its products for sale in the U.S.)

At the same meeting, FDA inspectors said their recommendation to approve Sovaldi would be "based on" removing an unnamed drug ingredient manufacturer from the application and "a determination that Gilead Foster City has an acceptable cGMP [current good manufacturing practices] status."

Records show the FDA didn't issue a warning letter or otherwise delay the approval process when Foster City failed its inspection.

Instead, the Sovaldi preapproval inspection started four days later and lasted two weeks. At the end, inspectors issued Foster City another 483, this time with 15 violations, formally outlining problems and requiring a written plan to fix them. Inspectors said they couldn't recommend Sovaldi's approval.

FDA officials gave Gilead two options during an Oct. 29 teleconference: Remove Foster City, a "major testing site" for Sovaldi, from the application, and use a third-party contractor instead; or use Foster City but hire another firm to monitor the site and sign off on its testing work.

Gilead was optimistic. “Based on recent communications with the FDA, we do not expect these [inspection] observations to delay approval of sofosbuvir,” the company said in its Oct. 31 SEC filing.

Gilead chose to replace the Foster City plant with a contract testing site, federal records show. By December, Sovaldi was approved for distribution, and the company soon announced its $1,000-per-pill price tag.

Not Just Generics

Recent media reports, and the ongoing recall of the widely used blood pressure medicine valsartan, have led consumers — and members of Congress — to question whether generics are manufactured safely. Valsartan pills made in China and India were found to contain cancer-causing impurities.

Branded-drug quality, in large part, has been spared from congressional scrutiny. But many factories — overseas and in the U.S. — make branded and generic drugs.

In January 2018, FDA inspectors hit a Korean manufacturing plant that makes Ajovy, a migraine drug, with a warning letter. With the problems still unresolved in April, an agency reviewer recommended withholding approval. When they returned in July, inspectors wanted to give the plant the worst possible classification: “Official Actions Indicated.” Among other problems, inspectors found that glass vials sometimes broke during the manufacturing process and that the facility lacked protocols to prevent the particles from getting into drug products. The FDA’s Office of Manufacturing Quality eventually downgraded the inspection to just “Voluntary Actions Indicated.”

The drug was approved in September 2018 and priced at $690 a month. FDA records indicate no further disciplinary action was taken. Teva, the maker of Ajovy, did not respond to requests for comment.

Similarly, when FDA inspectors visited a contract manufacturing facility in Indiana used to make Revcovi, which treats an autoimmune disease, they noted that a redacted drug lot had failed a sterility test because the vials tested positive for a bacterium called Delftia acidovorans, which can be detrimental even in people with healthy immune systems, studies show. But the drug-filling machine stayed in use after the contaminant was discovered, the FDA determined. Inspectors recommended withholding approval.

The drug was approved in October 2018 even after another inspection turned up problems, with a list price of $95,000 to $189,000 per month for an average patient, according to health care data firm Connecture.

Revcovi’s manufacturer, Leadiant Biosciences, said through an outside public relations firm that its contract manufacturer’s written responses to the FDA observations were considered “adequate” by two FDA offices, adding, “We do not have any more information to share with you at this time

as pharmaceutical manufacturing processes are confidential."

Problems with drugs can take years to discover — and then only after patients are injured. So, many health researchers say, more caution is warranted.

"They're doing so few of these [FDA] inspections pre-market," said Diana Zuckerman, president of the nonprofit National Center for Health Research. "The least they can do is listen to the ones they're doing."

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