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## THE WALL STREET JOURNAL

**Bitter Pill: How a Drug Firm Paid For University Study, Then Undermined It --- Research on Thyroid Tablets Found Cheap Ones Were Just as Good as Sponsor's --- Article Pulled at Last Minute**

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SAN FRANCISCO -- It was one of those impenetrable research papers full of statistics and six-syllable words. But its stark conclusion could have cut medication costs for millions of people and might have disrupted a billion-dollar deal.

If only it had been published.

The paper concerned a drug called **Synthroid**, the main product of British pharmaceuticals company and drugstore chain Boots Co. **Synthroid** is taken daily by about eight million Americans to control hypothyroidism, a metabolic disorder. It dominates the \$600 million U.S. market, so much so that when Boots put its drug division up for sale, Germany's BASF AG agreed to pay a lofty price of \$1.4 billion for it.

**Synthroid** has a lock on the U.S. market because makers of rival products have long been unable to resolve doubts that their pills work exactly the same -- that they are "bioequivalent." Many doctors have remained leery of using the rival drugs even though they cost about half as much or less.

But just as Boots and BASF were about to seal their deal, an authoritative demonstration of bioequivalency was at hand.

A research team headed by Betty **Dong** at the University of California at San Francisco had concluded that **Synthroid** and three cheaper drugs were essentially interchangeable. The study had withstood extensive review by experts at UCSF not connected with it.

The Journal of the American Medical Association accepted for publication Dr. **Dong's** paper on the study, in which she concluded that U.S. health-care costs could be cut by \$356 million a year if **Synthroid** were replaced by the cheaper but equally effective drugs. The piece had the potential to "change the way physicians practice," says David Cooper, associate professor and director of the thyroid clinic at Johns Hopkins medical school, who is a JAMA contributing editor.

He won't discuss JAMA's review of the study. But the medical journal rigorously vets submissions -- this one was peer-reviewed by at least five outsiders -- and its acceptance is a strong endorsement of scientific validity. JAMA planned to publish the study in its Jan. 25, 1995, issue. Page proofs were at the printer. But the article never ran. The reason stems from the fact that the study's sponsor, after paying \$250,000 to finance the research, aggressively strove to discredit it and suppress its conclusions.

The study's sponsor was Boots.

The **Synthroid** affair illustrates what some leading scientists decry as increasingly frequent corporate attacks on open scientific debate, at a time when industry-supported research is crucial because of a shrinking government role in medical research.

In a recent article in the New England Journal of Medicine, Steven A. Rosenberg, chief surgeon of National Cancer Institute, cited what he said were four instances of promising research being squelched or slowed by corporate sponsors' demands for secrecy to preserve possible competitive advantage. It is an "insidious problem," he wrote, one that "has escalated dramatically in the past decade and is impeding the progress of medical research."

Boots says it had a contractual right to prohibit publication of the research and did so for scientific, not business, reasons. It contends the study's conclusion was invalid because of numerous missteps in managing patients and analyzing data, and argues that because UCSF officials were unwilling to intervene, it had no choice but to take a hard line. "I did what I had to do," says Carter Eckert, who launched the study while a Boots executive. "I stopped a flawed study that would have put millions of patients at risk."

Leslie Benet, chairman of UCSF's biopharmaceutical sciences department, scoffs at this. "The Boots people did everything they could to make sure this study didn't get published because it was detrimental to their company," he says.

Boots's deal with BASF went through a year ago, and its former drug division is now part of Knoll Pharmaceutical Co., a BASF unit in Mount Olive, N.J. Boots says the research was disclosed and discussed in the sale negotiations. Mr. Eckert, now president of Knoll, says he didn't learn of JAMA's intention to publish the study until he was approached by The Wall Street Journal two months ago.

Nearly a year ago, however, Knoll's medical-research director wrote to JAMA listing alleged flaws in the study and saying the journal should have concerns about publishing it.

Hypothyroid patients don't naturally produce enough thyroid hormone and suffer such symptoms as lethargy, stiffness and low tolerance for cold. Drugs for them basically consist of the hormone itself, called levothyroxine. Natural hormone treatments were widely used before the Food and Drug Administration began requiring clinical-trial data to approve drugs in the 1930s. So when **Synthroid**, the first synthetic version of the hormone, was introduced in 1958, the FDA didn't ask the maker to submit trial data.

**Synthroid**, heavily marketed yet unpatented, quickly became the thyroid drug of choice. Nearly four decades later, it has 84% of the U.S. market, protected by something more durable than a patent: the bioequivalence barrier.

Makers of rival thyroid drugs contend they are bioequivalent -- that is, absorbed in the blood in precisely the same way as **Synthroid**. FDA endorsement of such a claim would be great for them. But the FDA lacks benchmark data on **Synthroid** needed to evaluate such claims.

There is a potential way around this: state-drafted lists of eligible drug substitutes. If a low-priced drug can land on these "formulary" lists, its use grows, because doctors and pharmacies are under pressure -- and in some states required -- to use the cheapest ones.

A decade ago, the maker of a rival thyroid drug called Levoxyl began claiming bioequivalence and pushing to get on the formularies. "Frankly," Mr. Eckert says, such claims "threatened our business. As a businessman, I had to do something about it."

That was when he decided to finance a comparative study of several thyroid drugs -- one designed to be definitive. Dr. **Dong**, a clinical pharmacist who is now 47 years old, seemed an ideal scientist to lead it. She had published articles on the risk of switching patients from brand-name versions of thyroid hormone to generics. Boots commissioned her to lead a six-month human study of **Synthroid**, Levoxyl and two

generic versions.

But within the 21-page research contract was one clause that later became critical. The study results, it said, were "not to be published or otherwise released without written consent" of the company.

This clause violated UCSF policy. Dr. **Dong**, who won't discuss details of the study itself, now says she shouldn't have signed the clause and did so naively. She had consulted colleagues, but not a lawyer. Still, for a long time, the publishing-rights clause caused no trouble.

Other problems did pop up, however, and soured the atmosphere. In 1989, while the 24 study subjects were still being enrolled, Massachusetts was moving to become the second state (after New Jersey) to add Levoxyl to its formulary. To fight that, Boots asked Dr. **Dong** for preliminary test-tube data from her study.

Disclosing such data would wreck the blind-testing procedures used to prevent bias, and clinical-trial experts say it is justified only if patients are endangered. But Boots made the request repeatedly, and Dr. **Dong** "adamantly refused," her records show. The researchers were angered, and the collaborative tenor of the undertaking began to deteriorate.

After that, the study went mostly as planned, with snags hashed out during Boots's many site visits, researchers say. In late 1990, Dr. **Dong** and her team finished collecting information and, at the company's request, turned it over to Boots. The presentation left the four tested drugs unidentified. But that didn't really matter, because the result was obvious: The four were bioequivalent.

Boots came out swinging. Gilbert Mayor, who was Boots's medical-services director, fired off several letters to Dr. **Dong** raising for the first time broad objections to the execution of the study. The list, compiled by the company in a thick binder, initially focused on the way investigators assigned patients to receive each drug and how faithful patients were in taking them. More queries followed. Eventually, Boots raised a host of objections to the study, including variations in pill potency, the length of time blood samples were stored, and several other technical matters. According to researchers' records, Boots eventually raised 136 questions related just to patients' case-report forms.

Unsatisfied with Dr. **Dong**'s responses, Dr. Mayor proposed a meeting with the UCSF team. Dr. **Dong** declined, noting that the team was still analyzing data and adding: "As always, we intend to publish this study in a reputable medical journal." Boots insisted that the alleged flaws be corrected before publication.

The company's position hardened. In June 1991, Dr. Mayor wrote to Dr. **Dong**'s division head that "we believe this study, because of its many difficulties, should be terminated."

When that approach failed, the company hired consultants. Jerome Hershman, a thyroid expert from UCLA, concluded that "the execution of the study was flawed seriously," so that any conclusions would be "compromised." A Harvard bioethicist, William Curran, cited "a disturbing number of questionable practices by the investigators."

But both experts qualified these comments by noting that Boots was their sole source of information. Boots did include at least some of Dr. **Dong**'s responses to its concerns, but neither expert contacted her. And their review of data wasn't complete. Dr. Hershman, for example, examined the records of only three of the patients, his report to Boots states, although he believes he had an adequate basis to reach his conclusions. (Dr. Hershman also received fees from Boots for lectures and for serving on its Thyroid Research Advisory Council, but he says his ties to Boots "in no way influenced" his conclusions.)

Dr. Curran says he "had no view on the ethics of the study" and was chiefly concerned with getting the parties together to settle their differences.

Meanwhile, Scott Fields, an investigational drug pharmacist and a member of the UCSF committee

overseeing clinical trials, also probed the alleged deficiencies, at Dr. **Dong's** request. In a June 1992 memo, he called most discrepancies "minor and easily correctible" and concluded: "It would be extreme hyperbole to question the scientific merit of the study on the basis of these deficiencies."

After a Boots meeting with UCSF officials, Dr. **Dong's** superiors had her work reviewed by Dr. Benet, a noted expert in comparative drug analysis. He met with Boots and corresponded at length, and finally concluded that almost all of the company's criticism was unwarranted.

Dr. Benet notes that Boots reviewed early drafts of the study, and it was revised to address some of the company's concerns. He says Boots faulted Dr. **Dong** for failing to follow some procedures even though the study's guidelines didn't specify them. For example, he says, Boots complained that her team didn't collect certain patient test data that forms prepared by Boots itself hadn't called for. "The Boots people were deceptive and self-serving," Dr. Benet says.

In January 1994, with painstaking data analysis finally complete, Dr. **Dong** sent a final draft of her manuscript to Boots. The company's alarm is recorded in notes that Steve Freeman, vice president of marketing, wrote on a copy of her cover letter. Among his comments: "Clearly bioequivalent according to the traditional bioavailability standards and the parameters established by the FDA (the analysis method was very conservative as well)." He also wrote: "tackle therapeutic-equivalence issue head on -- are definitely therapeutically equivalent -- plays into Levoxyl." At the top of the page, under "Actions," Mr. Freeman wrote: "must review harshly" and "begin to get our ducks in order with the salesforce."

Mr. Freeman didn't return calls seeking comment. Mr. Eckert, when presented with a copy of Mr. Freeman's notes, says they were merely his "outline of the paper." He says Mr. Freeman filed the notes away without acting on them.

But other Boots executives did act. Neil Kurtz, a senior vice president, wrote a letter to Dr. **Dong** that, among other things, asked that Boots be told of any conflicts of interest she might have. The letter said Boots had offered to sponsor a second study (a process that would take years) and ended by stating: "As a partner in this study, we believe that it will be necessary to use all legitimate, honest, honorable, and ethical means at our disposal to inform the scientific and regulatory community of the problems with this study if you choose to pursue publication of this manuscript."

The university stood its ground. It sternly rebuffed the conflict-of-interest suggestions. Dr. **Dong** wrote back that she always intended to tell JAMA of Boots's objections, and added bluntly: "It is our view that Boots rejects the analysis originally agreed upon because it does not like the results."

Boots now hired investigators Kroll Associates, which petitioned UCSF for any information on financial or nonfinancial support provided to Dr. **Dong**, her division and the School of Pharmacy. Mr. Eckert says Boots had reason to believe someone at UCSF had leaked information about the study to the maker of Levoxyl, Daniels Pharmaceuticals Inc. of St. Petersburg, Fla. He says the investigation was "inconclusive."

Mr. Eckert agrees such measures were extraordinary but says they were necessary because Dr. **Dong** and UCSF couldn't be persuaded. He says the study's flaws wouldn't have been apparent, even to an expert reviewer at JAMA, from the manuscript alone. In his view -- one shared by some thyroid experts -- switching drugs without testing to ensure proper dosage can lead to "subtle symptoms" like changes in heart rate and energy level. Other experts say drug substitution poses an inconsequential risk to hypothyroid patients, most of whom are regularly tested anyway.

"Everything we did was aboveboard and ethical," Mr. Eckert says.

The struggle went on. In a September 1994 letter to UCSF, Boots's Dr. Kurtz said Boots was troubled by "the obvious tilt of this manuscript in favor of Daniels Pharmaceuticals' marketing position." But Mr. Eckert says he had initiated the study back in 1986 primarily "to find out what the truth was" on bioequivalence, adding that the answer still eludes him: "I have no evidence one way or the other."

Yet Boots did seek to shape the answer. In November 1994, Boots's Dr. Mayor wrote Francis Greenspan, a noted endocrinologist at UCSF who was one of the researchers on the study, and proposed "some conceptual changes" in the manuscript. The revised paper would cite contradictory evidence on bioequivalence and stop short of recommending drug substitution. "If you accept this concept, we would be very happy to work with you on new revisions of the manuscript," Dr. Mayor wrote.

Dr. Greenspan says the changes were a clear attempt to induce UCSF to water down its conclusions in exchange for Boots's allowing publication. Dr. Mayor declines to comment on that. Dr. Greenspan says the proposal was unacceptable to Dr. **Dong** and to him. "We were both sick about it," he says. "It was really worth their while to snuff this thing out."

All these efforts by Boots to block publication of the study it sponsored had failed. But the company still had an ace: the publishing-rights clause.

Dr. Greenspan says Dr. Mayor twice raised the possibility of a lawsuit based on the clause. The researcher cites dates and settings where he says this happened. He says that Dr. Mayor, when reminded that such a suit might bring bad publicity to Boots, replied that the company would be hurt more if the study got out. Dr. Mayor "categorically" denies he ever mentioned suing.

In the first week of 1995, Dr. **Dong**, bedridden with the flu, got a call from an aide to UCSF's newly appointed attorney, Shelley Drake. The aide urged Dr. **Dong** to comply with the publishing-rights clause, reversing the stand taken by the previous UCSF attorney, people familiar with the matter say. Defy it, the aide warned, and Dr. **Dong** and the article's six co-authors would have to defend themselves in court -- with no help from the university.

Dr. **Dong** hastily consulted her co-authors. They had worked on the project for some eight years, and they were dismayed by the university's sudden about-face. None could afford lawyers in a lengthy dispute. "We weren't willing to take that risk," she says.

So Dr. **Dong** telephoned the Journal of the American Medical Association. She instructed its editors to pull the plug on the thyroid article.

Joseph Cowan, UCSF attorney before Ms. Drake, is critical of the university's change of heart. "By not standing up to Boots, the university let the whole faculty down," he charges. Ms. Drake and the dean of the pharmacy school, George Kenyon, say in a statement that UCSF considers academic freedom a critical value, but "the difficulty here is weighing the right to publish against a likely claim against the university for breach of contract and the possibility of significant damages.

The sale of Boots's drug division to BASF closed on schedule in April 1995. BASF says it "was fully aware of all the activities related" to the UCSF study prior to the closing. Mr. Eckert says he can't speculate on how publication of the study by JAMA as planned might have affected the sale, noting, "It's a hypothetical question."

But drug-industry analyst Hemant Shah, after being informed of the article's conclusion, says publication would have been a "disaster" for Boots. "It could have substantially lowered the valuation of the transaction and accelerated the decline of the brand," he says.

Midway through the **Synthroid** study, Massachusetts went ahead with its plan to add Levoxyl, the **Synthroid** rival, to its formulary. But Knoll has tried to dissuade the state's doctors and pharmacists with ads declaring that "there is no substitute for **Synthroid**." The Massachusetts Pharmacy Journal calls the ad "misleading" and won't run it.

As for Dr. **Dong**, for months she held out hope of still publishing the article. But then last June the American Journal of Therapeutics -- a peer-reviewed publication of which Knoll's Dr. Mayor is an editor -- ran a 16-page critique of her unpublished work, saying it was too flawed to reach any conclusions about

bioequivalence. The lead author: Dr. Mayor himself.

This repudiation of Dr. **Dong**'s methodology and the complete reinterpretation of her unreleased data, the equivalent of a scathing theatrical review before opening night, almost certainly prevents her from ever publishing the original paper, says her colleague Dr. Benet. "It was a very sad experience," he says.

It is an experience that Dr. **Dong** says has persuaded her never again to undertake research sponsored by a drug company.

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