The New York Times

Madison Ave. Has Growing Role In the Business of Drug Research

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Abstract (Summary)

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Full Text (3807 words)

Dentists leafing through The Journal of the American Dental Association last May found a study concluding that a new drug called Bextra offered relief from one of their patients' worst nightmares -- the acute pain that follows dental surgery.

Federal regulators had rejected that conclusion only six months before, leaving Bextra's marketers, Pharmacia and Pfizer, hard pressed to sell it as an advance over Celebrex, their earlier entry in a crowded market for pain drugs.

The new study helped light a fire under Bextra. Its sales soared 60 percent over the three months that followed, according to industry data. But the research was not conducted by academics. Instead, the lead investigators were from Scirex, a little-known research firm owned partly by Omnicom, one of the world's biggest advertising companies.

Madison Avenue -- whose television ads have helped turn prescription medicines like Viagra, Allegra and Vioxx into billion-dollar products -- is expanding its role in the drug business, wading into the science of drug development.

The three largest advertising companies -- Omnicom, Interpublic and WPP -- have spent tens of millions of dollars to buy or invest in companies like Scirex that perform clinical trials of experimental drugs. One advertising executive calls it "getting closer to the test tube."

Ad agency executives say they do nothing to distort the research process. But critics worry that science is being sacrificed for the sake of promotion. "You cannot separate their advertising and marketing from the science anymore," said Dr. Arnold S. Relman, professor emeritus at Harvard Medical School and a former editor of The New England Journal of Medicine. "Ad agencies are not in the business of doing science."

In interviews, advertising executives say their intention is to work side by side with scientists, directing research toward drugs the marketers think could be big sellers. Their companies, they say, can help design -- or as in Bextra's case even conduct -- studies aimed at showing that the drugs have the qualities patients most desire.

Armed with the results, ad agencies try to sway doctors' prescribing habits. Some agencies own companies that ghostwrite articles for medical journals. They also create the continuing-education courses that doctors take to maintain their licenses. As new drugs are about to go on sale, these marketers recruit doctors to speak to peers about the drugs' benefits, often at expensive dinners the physicians are paid a fee to attend.

"We provide services that go from the beginning of drug development all the way to the launch of your products," said Joe Torre, chairman and chief executive of Torre Lazur-McCann Healthcare WorldWide, an Interpublic unit that is among the biggest health care marketing companies.

Only a few years ago, drug research and education were the province of universities. But with pharmaceutical companies counting on instant blockbuster sales of their new drugs, executives found the university system too slow. And ad agencies -- having built a multibillion-dollar business selling drugs to consumers -- pushed deeper and deeper into the process.

Federal law prohibits the promotion of drugs before they have been approved by the Food and Drug Administration, or the promotion of them for unapproved uses. But published research and medical education are exempt from those rules, and doctors are free to prescribe approved drugs for any purpose.

The critics say that marketers are exploiting the loopholes, to begin building markets for expensive new medicines long before they win government approval and, later, to prompt physicians to prescribe drugs for conditions the medications are not approved to treat.

"Doctors are led to prescribe drugs that may not be necessarily worth the money, may not be better than a generic that's already on the market and that their patients don't need," Dr. Relman said. "It's clearly contributing to the rising costs of prescription drugs and health care."

Moreover, critics worry that the success of drug makers and marketers in spurring big sales shortly after a drug's approval means that millions of patients may take a drug before all of its side effects are known. Just last week, Pharmacia sent letters to thousands of doctors warning that Bextra can cause a life-threatening skin rash.

Advertising executives note that scientific trials are tightly regulated and that most medical journal articles get careful review. Doctors, they say, are hungry for information about new drugs.

"The implication that we are going to accentuate the good things and may bury the bad things -- there would be nothing in it for us to do that," said Lloyd J. Baroody, managing director of Target Research Associates, a research firm in New Providence, N.J., that Torre Lazur acquired in March. "I can't imagine why anyone in my company would want to break the law or go against F.D.A. regulations."

Even before ad agencies became involved in research, experts had found repeated cases in which the drug industry shaded the truth in its zeal to produce blockbusters. In a May 2000 article in The New England Journal of Medicine, Dr. Thomas Bodenheimer, a professor at the University of California at San Francisco, cited numerous cases in which, he said, drug companies manipulated results of clinical trials by controlling a study's design or choosing to make public only positive data.

The problems can only grow worse, he said, with ad agencies involved.

"It introduces another bias into the whole clinical drug trial picture," Dr. Bodenheimer said, "so that the American public and the physicians in the United States are not going to know, really, the true facts about the drugs."

The GhostwriterArticles That Follow Marketers' Advice

Executives at Novartis, the Swiss drug maker, faced a marketing conundrum last spring. They had watched sales slide for Ritalin, the company's drug for attention deficit hyperactivity disorder, as competitors came out with longer-acting versions.

Novartis had introduced Ritalin LA, its own once-a-day medicine. But there was no research to back up a crucial selling point: that the eight- to nine-hour impact of a dose -- long enough to help at school, but not too long to interfere with dinner and bedtime -- was better for many children than the 12-hour action of a competitor's drug.

The drug company's advisers at Intramed, a medical education company owned by the global ad giant WPP, had a solution. They would take an article, commissioned from two university professors, that objectively surveyed a wide range of drugs and rewrite it to emphasize the potential benefits of a drug with the characteristics of Ritalin LA.

"We would like to help draft this manuscript," Marcia Zabusky, a vice president of Intramed, told the doctors in a

conference call, according to a transcript of the conversation obtained by The New York Times, "and then submit it to you for your -- for your editing and for approval."

During the call, Shane Schaffer, a Novartis marketing executive, told the doctors that the company wanted "a quick, down and dirty" article. A study expected to provide scientific data showing Ritalin LA's advantages was not scheduled to start until the following day, he said, but the lack of research findings should not be an obstacle.

"Obviously, we have to stick within data limits of what's published currently as well as what we know are factual about these products," he told the doctors. "But, of course, inferences can be made."

One such "potential theoretical conclusion" of the article, Ms. Zabusky added, was that a drug that worked for 9 hours might be better than a 12-hour drug.

The doctors -- John S. Markowitz and Kennerly S. Patrick of the Medical University of South Carolina -- agreed to what Intramed and Novartis proposed. "I think we're quite clear on what you want the next manuscript to look like," Dr. Patrick said as the call concluded.

To produce the new draft, Intramed turned to Linda Logdberg, who has a doctorate in anatomy and has made her living the last 12 years as a ghostwriter for Intramed and other medical marketing companies. Starting with an outline approved by Intramed, Dr. Logdberg said that she produced a new manuscript in a few days.

The assignment was one of her last ghostwriting tasks. Dr. Logdberg, who recently took a job teaching biology to high school students, said that she had become increasingly disenchanted with the process.

Typically, she said, her manuscript would be sent to the drug company for approval before it was given to the doctors who were paid to be listed as the authors. Some doctors fretted over each comma, Dr. Logdberg said, while others made no changes at all. The marketing companies, she added, "will drop a doctor if they don't think he will be particularly malleable."

The result, Dr. Logdberg said, is marketing masquerading as science.

"I don't have any problem with medical advertising that states in a clear way, either by format or by copy, this is an advertisement," she said. "What I mind is advertising that calls itself education."

The ad agencies' medical education companies say that they neither toy with science nor ghostwrite articles that physicians use to make decisions about prescribing drugs.

"We make editorial suggestions," said Jed A. Beitler, chairman of Sudler & Hennessey, a division at WPP that includes Intramed. "The doctors are the ultimate writers."

Dr. Markowitz and Dr. Patrick agreed, saying that Intramed did not dictate what their paper should say. "No figure, no table, anything goes in without our approval," Dr. Markowitz said. Dr. Patrick added that he thought, based on past research, that a drug like Ritalin LA could be better for certain children than other long-lasting drugs.

Neither the doctors nor the companies disputed the accuracy of the transcript of their conference call.

Novartis said the article was not intended to conclude that one product was better than the others. Instead, the company said, it was a review of the available medications in which the authors could suggest theoretical advantages.

Mr. Beitler said that Intramed was unhappy with the manuscript that Dr. Logdberg produced and later gave the assignment to another writer. The article has not been published.

A 1998 survey of named authors writing for some of the nation's top journals, including The Journal of the American Medical Association, which published the survey, found that 11 percent of the articles had been ghostwritten. Some experts think the practice continues to grow, even as the best journals take steps to prevent it.

Wyeth hired ghostwriters in promoting the diet drug combination fen-phen, according to documents made public in litigation filed after it became evident that fen-phen caused a potentially deadly heart-valve defect. Evidence of ghostwriting has also surfaced in federal and state investigations of Warner-Lambert's marketing of Neurontin, an epilepsy drug, for more than a dozen unapproved uses.

One document made public in a whistle-blower lawsuit against Warner-Lambert describes how Proworx, a company owned by the ad giant Omnicom, offered to help write journal articles about using Neurontin to treat pain. Proworx planned to recruit doctors to be the named authors of the articles, paying them a $1,500 fee.

Omnicom declined to comment on the matter.

Dr. Relman, the former editor of The New England Journal of Medicine, said there was no place in medical education for ad agencies.

"We don't get anywhere in medicine without objective data," he said. "That's the coin of the realm. The whole purpose of medical research is lost if you don't tell the truth."

The Right ResultsFinding the Positive In Medical Studies

For Pharmacia and Pfizer's second run at proving that Bextra was effective against acute pain, the research firm Scirex headed to central Texas, where it recruited dozens of patients with impacted molars. In two studies, it reached just the conclusion that the drug makers' sought.

But three doctors who reviewed the Scirex studies for The Times said the research was not persuasive. All three said that one of Scirex's conclusions was insignificant: that one dose of Bextra worked longer than a single dose of a medicine containing oxycodone and acetaminophen, a combination often sold under the brand name Percocet. Patients rarely receive just one dose of that combination drug, the doctors said, because it wears off in four to six hours.

One of the doctors, Eric J. Topol, chairman of the Cleveland Clinic's department of cardiovascular medicine, called the studies "a contrived comparison" and said he found it "quite disquieting" that Scirex was partly owned by an ad agency.

"If this is where clinical research is headed, that would be a terrible negative trajectory," he said.

Dr. Topol -- who drew attention last year with a finding that Celebrex and its competitor, Vioxx, appeared to raise the risk of heart attacks -- said the Bextra studies did not include enough patients to justify drawing a broad conclusion. The average age of patients in the study, 23, did not represent the population likely to take the drug, he added.

Yet through publication in the leading dental journal, the research helped Bextra's marketers shift attention away from the F.D.A.'s negative findings. Because of confidentiality rules, the F.D.A. cannot release any information about the earlier pain studies that failed to sway regulators.

"Even though the study lacked some important proof, the real problem is that in the dental literature, this will be read," Dr. Topol said. "And dentists, who have to deal with trying to prevent or modulate pain, will be impressed."

Judy Glova, a spokeswoman for Pharmacia, said the drug company stood behind the design and conclusions of the Scirex studies. Pharmacia was not trying to bypass the regulatory process, she said, adding that the company is in discussions with regulators to have Bextra approved for acute pain.

Scirex executives did not return repeated phone calls.

Editors at The Journal of the American Dental Association said the Scirex article was reviewed by at least three scientists. One reviewer, Dr. Paul A. Moore, an associate editor of the journal, said the study was "carefully designed and rigorously performed."

But Dr. Moore said he would have recommended that the journal reject the paper had he known that Bextra was not approved for acute pain.

The Bextra episode is just one example of the changing face of drug research. In the early 1990's, about 75 percent of the drug industry's clinical research dollars went to universities, according to a study by CenterWatch, a company that tracks clinical trials. By 2000, just 34 percent went to academic institutions, while the rest went to investigators working under the direction of either a private research firm like Scirex or a pharmaceutical company.

Omnicom says it has no control over Scirex. "We have nothing to do with the design of clinical studies," said Pat Sloan, an Omnicom spokeswoman.

Yet when the ad agency paid $20 million for part-ownership of Scirex in 1999, a top Omnicom executive, Thomas L. Harrison, said he expected Scirex's research to produce positive results for drug company clients -- results that would help speed new-drug applications, or N.D.A.'s, to the F.D.A.

"Our goal," he said, "is to help ensure that all clinical studies and each patient accrued into a study can be assessed to support the N.D.A. submission."

The Invisible HandCourting Doctors With Food and Cash

To see just how successful the invisible hand of Madison Avenue can be, one need look no further than the introduction this summer of a new antidepressant called Lexapro by Forest Laboratories, a drug company based in Manhattan.

Competitors like GlaxoSmithKline, the maker of Paxil, and Pfizer, which makes Zoloft, have each spent tens of millions of dollars for television and print ads promoting their antidepressants. But Forest, a current darling of Wall Street, does not spend its money on consumer advertising.

Instead, it relies on WPP's Intramed and other companies to organize expensive dinners for physicians where research studies, many paid for by Forest, are discussed.

Just days after the F.D.A. approved Lexapro in August, Intramed and Forest invited Dr. Richard J. Brown, a Manhattan psychiatrist, and about 20 of his peers to dinner at Daniel, one of Manhattan's most expensive restaurants. Besides dining on tournedos of beef and cabernet sauvignon, each doctor was paid $500 for attending.

The industry's ethics rules say that any free meal for doctors must be at a restaurant considered modest by local standards. As for the $500, the federal government warned drug companies in guidelines proposed last month not to give gifts or cash to doctors in an attempt to influence their prescribing -- a practice it said would be illegal.

Mr. Beitler, the WPP executive, said the dinner and the $500 checks were appropriate because the doctors had been hired as consultants for the night to sit on Forest's advisory board. He said Daniel was not a restaurant his agency normally used. Intramed executives, he said, had scheduled the dinner at another restaurant that closed three days before the Lexapro meeting.

Dr. Brown, who is retired, said he did no consulting that night, or at other dinners he attended that were organized by Intramed and other drug marketing companies on behalf of their pharmaceutical clients.

"I think it's disgusting," said Dr. Brown, who organized a protest outside a similar dinner that Forest held at the Four Seasons last year. "This is my profession, and I hate to see this happening."

Two weeks after the dinner at Daniel, analysts at J. P. Morgan called Forest's introduction of Lexapro "an instant success." Based on the number of prescriptions written in Lexapro's first weeks on the market, the analysts said that Forest appeared on its way to one of the best new product launches in the industry's history.

"This market does respond to promotion," Kenneth E. Goodman, Forest's president, said in a conference call with Wall Street analysts on Oct. 15. Forest invested so much in promotion that Lexapro was the subject of 63 percent of all industry-sponsored meetings that primary care doctors reported attending in an October survey by ImpactRx, a consulting firm.

Indeed, the drug industry relies far more heavily on behind-the-scenes promotion than on consumer advertising. Last year, just $2.8 billion of the $11.8 billion the drug industry spent on marketing was aimed at consumers; the rest paid for everything from dinner meetings with doctors to sales calls and medical education, according to Verispan, a health-care information company.

For Forest and its ad agency partners, selling doctors on Lexapro is crucial.

Lexapro is not an entirely new drug, but rather a chemically refined version of Celexa, an antidepressant that accounts for 70 percent of the company's sales. Wall Street is counting on Forest to persuade doctors to switch Celexa users to Lexapro, because the older drug will lose its patent protection in 2004. Once the patent expires, Celexa sales will plummet, as generic companies begin offering low-priced versions of the drug.

But Forest can point to just one study concluding that Lexapro offers patients an advantage over Celexa -- a study that the company paid to have published, and has promoted at dinners like one Dr. Brown attended at a Manhattan steakhouse, just two weeks after the meal at Daniel.

The paper, by Dr. Jack M. Gorman, until recently a professor at Columbia University and now on the faculty of the Mount Sinai School of Medicine, pooled the results of three studies and concluded that Lexapro "may have a faster onset" than Celexa. Dr. Gorman's paper was published in CNS Spectrums, a medical journal he edits.

Forest said that it paid Medworks Media, a small medical marketing company that publishes the journal, to print Dr. Gorman's article in a special supplement.

Other researchers find the data less convincing. The Medical Letter, a nonprofit newsletter respected for its

independence from the pharmaceutical industry, reviewed the same clinical trials as Dr. Gorman and concluded in September that Lexapro had not been shown to be better than any other antidepressant, including Celexa.

Dr. Gorman said that Forest paid him as a consultant -- as drug companies do hundreds of other doctors -- but did not pay him for the Lexapro article. In published research, he has acknowledged serving as a consultant or receiving payments from a dozen other drug makers.

Last month, Forest and Intramed turned their attention to fourth-year medical students who will begin writing prescriptions next year.

On Oct. 18, Forest paid to fly one student from each medical school in the country to New York for a two-day conference at Columbia. The students were treated to two nights at the Plaza Hotel, three meals a day and tickets to a Broadway show. Intramed coordinated the event, shuttling students from place to place and helping conference speakers with their presentations.

Dr. Gorman, who helped organize the conference for Columbia, gave a brief presentation on his Lexapro study during a speech about antidepressants. He said the conference's purpose was to get medical students interested in psychiatric research and in residency positions at Columbia, not to promote Forest's drugs. Forest had simply donated money for the conference, he said.

The University of Rochester did not send a representative because some students expressed concern about the drug industry sponsorship. In a letter to Columbia, Lenard I. Lesser, a Rochester medical student, said that Forest would not have paid for the conference unless it expected a financial return.

"This is setting a bad precedent," Mr. Lesser said. "It is all about establishing relationships that will be profitable."

The tide does not appear to favor Mr. Lesser's stance. In Washington, the F.D.A.'s new chief counsel, Daniel E. Troy, who fought restrictions on drug promotion as a private lawyer, is leading a review of regulations that could relax existing limits on behind-the-scenes marketing of drugs.

A television report based on this article will be broadcast tonight on the PBS program "Now With Bill Moyers" (9 p.m. on most local stations).

[Photograph]
A Medical Student Takes a Stand -- Lenard I. Lesser, a medical student at the University of Rochester, criticized drug industry sponsorship of a recent conference at Columbia. (Will Yurman for The New York Times); A Former Insider Speaks Out -- Linda Logdberg, a former ghostwriter for medical marketing companies, says many of the companies try to disguise marketing as science. (Bobby Abrahamson for The New York Times); A Critic Sees Manipulation -- Dr. Thomas Bodenheimer of the University of California at San Francisco has been critical of drug company involvement in clinical trials. (Dan Krauss for The New York Times)(pg. C4)

[Chart]
"The Behind-the-Scenes Push to Sell Drugs"
Most of the money spent promoting drugs is invisible to the public. Last year, the drug industry spent $9 billion on behind-the-scenes marketing, versus the $2.8 billion spent advertising drugs directly to consumers.
DRUG PROMOTION SPENDING
Graph shows the amount of money spent promoting drugs using the following methods since 1996:
DIRECT MARKETING
CONSUMER ADVERTISING
BEHIND THE-SCENES MARKETING
ADS IN MEDICAL
JOURNALS MEETINGS
SALES CALLS TO DOCTORS AND HOSPITALS
(Source: Verispan)(pg. C4)

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