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# JOURNAL SENTINEL

## Side Effects

**A Journal Sentinel Watchdog Report**

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By John Fauber

With universities tightening up their ethics policies, drug firms are turning to private physicians to promote their products.

# An Rx for bias?

By JOHN FAUBER  
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When looking for a doctor to travel the country and tout its costly prescription fish oil pill, GlaxoSmithKline didn't select a heavyweight university researcher.

Instead, it wrote checks to Tara Dall, a Delafield primary-care doctor who entered private practice in 2001.

For just three months of speaking engagements last year, GlaxoSmithKline paid Dall \$45,000, ranking her among the most highly paid of more than 3,600 doctors nationwide who spoke for the company, which released records for only one quarter of the year.



**Dall**  
Pushes fish oil

The practice of doing promotional speaking for drug companies has come under fire in recent years.

Critics say the talks can be biased and contribute to spiraling health care costs by promoting the use of expensive brand-name drugs over generics. The practice, according to critics, also leads to more non-approved and potentially harmful use of those drugs, so-called off-label prescribing.

For years, drug companies sought out influential university doctors with impressive credentials to bring their message to other doctors and persuade them to write prescriptions for their products.

But companies have been forced to back away from that approach as a growing number of medical schools, including the University of Wisconsin-Madison, have developed conflict-of-interest policies that ban such talks.

So much money is at stake that in January one academic doctor resigned his job at Harvard rather than give up his speaking income.

The problem: While medical schools can restrict biased speaking and require doctors to fully inform patients of their ties to drug companies, there are no such restrictions or requirements on private doctors.

"There are no skids on them," said Jerome Kassirer, former editor of the *New England Journal of Medicine* and a critic of the practice. "There is no way to control their participation."

Dall hedged when asked in an interview if she fully disclosed her financial relationship with GlaxoSmithKline to all the patients for whom she prescribes the company's high-priced fish oil product, known as Lovaza.

"I think I would (disclose) if I was going to do anything off-label," she said. "Whether I tell every single patient, I'm not sure."

The next day she called back and made a short statement, but hung up without answering questions.

"It is absolutely disclosed to patients that I am a speaker and that I speak for pharmaceutical companies, and it is listed on my Web site," she said.

## Little revealed

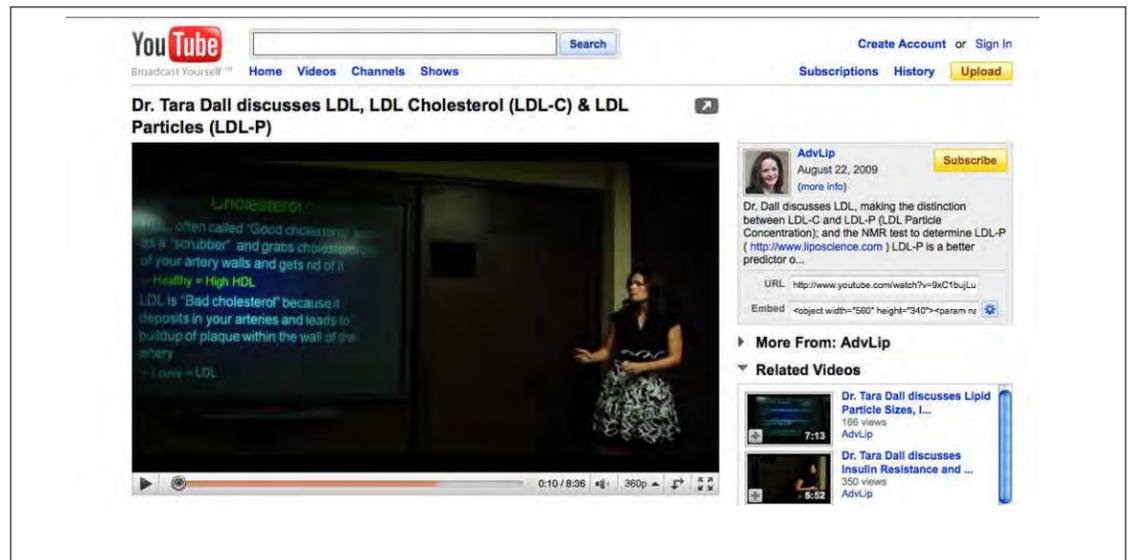
Last year, the *Journal Sentinel* series "Side Effects" found that there was little disclosure to patients of drug-company moonlighting among dozens of doctors at the UW School of Medicine and Public Health.

That led to a ban on promotional drug speaking, although UW doctors still can make large sums of money from device companies or serving as consultants. And signs were posted at the UW medical facilities informing patients their doctor may have a financial relationship with a drug or medical device company and telling them the details will be provided if requested.

According to her résumé, Dall does talks for five other drug and medical companies in addition to GlaxoSmithKline as well as community talks, including an unpaid speech on heart disease she gave to General Electric Co. employees in Wisconsin last August.

There, she made an eyebrow-raising statement about heart disease.

"As soon as we identify what puts you at risk, we can absolutely fix it," Dall assured them in the talk,



a video of which is posted on her Web site. "We can totally prevent cardiovascular disease from happening. We can completely trump genetics."

That's wrong, according to Steven Nissen, chairman of cardiovascular medicine at the Cleveland Clinic, and Raymond Gibbons, a professor of medicine at the Mayo Clinic in Minnesota.

At best, cholesterol-controlling statin drugs reduce heart attacks and strokes by about one-third, Nissen said.

"We cannot trump genetics," Nissen said. "If she was right, we could wipe this disease out just by giving drugs to people. Even if we put statins in the water supply, cardiovascular disease would still be the leading cause of death."

Even with optimal drug therapy as well as proper diet, exercise and weight, one-third of cardiovascular disease still would occur, added Gibbons. "We would like for there to be something to prevent cardiovascular disease from happening," he said. "There is not."

Dall did not respond to several requests to explain the comment.

Additionally, during the same speech, Dall referred to the advanced lipid test of another company that pays her to speak, but she did not disclose that financial relationship to those in attendance, said GE spokesman John Wheeler.

## Paid the most

At \$45,000, Dall received the most from GlaxoSmithKline among Wisconsin doctors during the three-month period for which records were released. That ranks her in the top 30 of about 3,600 doctors from around the country who were paid as speakers by GlaxoSmithKline.

She was paid up to \$3,000 a talk and spoke 15 times in the three-month period, the company said. In the last year, Dall said, she has given at least 60 lectures, and probably more, about Lovaza.

U.S. Sen. Herb Kohl (D-Wis.) has co-introduced legislation requiring companies to release payments to doctors to highlight conflicts of interest for the public. With the bill pending, GlaxoSmithKline and at least three other companies have begun listing payments to doctors. These lists, which look only at 2009, provide the first glimpse at the extent of the massive marketing of drugs and financial ties between doctors and drug companies.

About 45 doctors from Wisconsin got payments from GlaxoSmithKline of at least \$1,000 during the quarter for which the company released records. All but 10 of them were private-practice physicians.

Nationally, only eight doctors among the top 25 paid speakers had full-time university positions.

At least three other firms — Merck, Eli Lilly and Cephalon — also have listed payments to doctors for parts or all of 2009 activity.

Together, the lists show that more than 10,000 doctors and other health care professionals from around the country, including more than 125 from Wisconsin, were moonlighting for the four companies at some point in 2009, according to an analysis

## WHAT SHOULD PATIENTS DO?

Patients should feel free to ask their doctors not only if they have a financial relationship with a drug company, but how much they are paid, said Vera Hassner Sharav, president of the Alliance for Human Research Protection, a group that advocates for patients and others.

The question may anger some doctors, she said, but if the doctor is prescribing a drug made by a company for which he or she works, the patient has the right to know.

When there is a financial relationship, she said, patients should ask, what is the evidence that it is the best drug for them?

Better yet, try to find a doctor who doesn't have a conflict of interest, said physician Marcia Angell, a lecturer at Harvard Medical School and former editor of the *New England Journal of Medicine*.

And be wary of free samples, which often are the newest and most expensive brand name drugs, she said.

After the free samples are gone, both patients and doctors are hooked . . . and patients or third parties have to pay for them," Angell said.

## THE LOVAZA PARADOX

Doctors say there are plenty of over-the-counter supplements that have as much or more of the omega-3 fats EPA and DHA as GlaxoSmithKline's prescription fish oil, Lovaza. The problem is in health care regulations.

Equivalent over-the-counter supplements would cost up to \$300 a year.

Lovaza, because it's a prescription drug, is covered fully or in large part by health insurance.

So while it costs about \$2,400 a year, patients whose health insurance covers Lovaza might actually save money.

by the *Journal Sentinel*.

Near the top of Lilly's list of Wisconsin doctors was Rod Halvorsen, a private practice obstetrician/gynecologist in Manitowoc who got \$61,000 during the first nine months of 2009.

Halvorsen said he gives talks involving Lilly's osteoporosis drugs, Evista and Forteo, as well as about osteoporosis in general.

He said he has a passion for the topic because his mother died as the result of osteoporosis.

"I don't do this for the money," he said.

When he prescribes Lilly-manufactured drugs for his patients, Halvorsen said, he does not tell all his patients he is a paid speaker and consultant for the firm.

Lilly's disclosure of doctor payments is part of a 2009 settlement of a U.S. Department of Justice investigation of its marketing of its anti-psychotic drug, Zyprexa, which was being promoted for elderly dementia patients when it was approved only for schizophrenia and bipolar disorder.

“Obviously we are required to do it, but Lilly believes it is important to be transparent,” said Lilly spokeswoman Carole Puls.

The company also agreed to pay \$1.4 billion to settle criminal and civil investigations.

Like Lilly, Cephalon’s agreement to list doctor payments stemmed from a federal government investigation of illegal, off-label marketing of drugs, including the use of medical professionals who spoke to other doctors. The company also had to pay \$425 million to settle criminal and civil cases.

Unlike Lilly’s osteoporosis drugs, which are available only by prescription, doctors say there are plenty of over-the-counter supplements that are just as good as GlaxoSmithKline’s prescription fish oil, Lovaza.

Lovaza sales jumped from \$140 million in 2006 to \$679 million in 2009 (through November), according to data supplied by IMS Health, a drug market research firm.

William Davis, a Milwaukee cardiologist, said Lovaza is not worth the money.

Davis said at least six over-the-counter products have as much or more of the omega-3 fats EPA and DHA as Lovaza. All of them can be purchased for a fraction of the price, he said.

Lovaza, which has not been shown to reduce heart attacks or strokes, costs about \$2,400 a year at Walgreens in its FDA-approved dose of 4 grams a day. Similar non-prescription products can be purchased for about \$200 to \$300.

But basic health care math is pushing some consumers to opt for Lovaza over the much cheaper non-prescription fish oil, Davis said.

That’s because, while insurance doesn’t cover the cost of supplements, it may cover all or the vast majority of a prescription, meaning Lovaza actually costs patients less out of pocket.

“Sadly, that’s the logic,” Davis said. “People are saying, ‘Screw it, I’ll just have my insurance pay for it.’ It’s a house of cards.”

GlaxoSmithKline touts Lovaza as being free of mercury and other contaminants. But so are most over-the-counter fish oil products, according to an analysis by ConsumerLab.com.

“They are clean, and they deliver what they say they are going to deliver,” added Penny Kris-Etherton, a professor of nutrition at Pennsylvania State University.

Lovaza was approved to treat people with very high triglycerides. However, that’s a tiny portion of the population, 1.7% of Americans.

And GlaxoSmithKline acknowledged a lack of studies showing that treating high triglycerides reduces heart attacks and strokes.

GlaxoSmithKline said it does not seek private doctors over other health care professionals. But the company acknowledges its speaker program has been affected by new conflict-of-interest restrictions put in place by universities.

The company looks for respected, qualified experts who are good presenters, said spokeswoman Mary Anne Rhyne.

“Sharing information on complex disease states is important to advancing patient care, and health care professionals often learn best from their peers and colleagues,” she said in an e-mail.

### **Trend reversed**

Years ago, drug companies often enlisted private doctors for speaking, but in recent years influential university doctors became the preferred promotional speakers, said Kassirer, the former New England Journal of Medicine editor.

“Now it looks like it’s going back,” Kassirer said.

There has been a clear trend to ban or restrict the practice at leading academic centers, including UW, Harvard, Stanford, Duke and the University of Pittsburgh, said Ann Bonham, chief scientific officer at the Association of American Medical Colleges.

Within five years, she predicted, most medical schools will take such action.

In 2008, the association issued a report strongly discouraging academic doctors from doing drug company speaking.

In January, the issue took an unusual twist when Boston doctor Lawrence DuBuske resigned his Harvard position rather than give up his speaking. DuBuske got \$99,000 from GlaxoSmithKline in three months last year, more than any other doctor in the country.

In the past, drug companies had threatened to use more private doctors if medical schools restricted speaking, said Susan Chimonas, co-director of the Center on Medicine as a Profession at Columbia University.

Nissen, of the Cleveland Clinic, said he believes fewer university doctors are doing drug company speaking because he has been getting more and more fliers for dinner talks in which the speakers are private physicians.

Either way, such speaking is a problem because doctors are being used to boost sales, Nissen and Chimonas said.

Doctors can get dropped as speakers if they don’t properly promote a company’s drugs, Chimonas said.

Still, for a variety of reasons, large numbers of doctors continue to do the talks.

“I think it is money,” Chimonas said. “I think it is ego. Some of them think they are doing a good thing. They clearly are being used.”

### **More on Dall**

Rhyne, GlaxoSmithKline’s U.S. director of media relations, described Dall as highly respected with significant experience in her field of clinical lipidology, which involves treating lipid abnormalities such as un-

healthy cholesterol, triglycerides and related problems.

She said Dall brings a unique perspective as the medical director of one of the few lipid clinics in the country.

Dall sees patients at her office in Delafield, although in a brief interview she said she travels around the country and gives speeches two to three days a week.

While many doctors boast of articles in medical journals, Dall’s site notes she was featured in an ad in the Journal of Clinical Lipidology.

When it comes to published studies in peer-reviewed medical journals, there was little to be found for Dall.

She is listed as the lead author in a positive 2009 review article involving Lovaza. However, manuscript preparation for that study was supported by GlaxoSmithKline. And editorial assistance for the article, which was published in the peer-reviewed Southern Medical Journal, was provided by DesignWrite of Princeton, N.J.

DesignWrite is a medical communication company that previously had been linked to ghostwriting medical articles.

GlaxoSmithKline spokeswoman Rhyne said the article was initiated in 2007 when Lovaza was marketed as Omacor by Reliant Pharmaceuticals, which was bought by GlaxoSmithKline in December 2007. Rhyne said the article was reviewed only for accuracy.

Though GlaxoSmithKline and DesignWrite were involved, Dall said she and her co-author put hundreds of hours of work into the article.

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*John Fauber reported this story in a joint project of the Journal Sentinel and MedPage Today. MedPage Today provides a clinical perspective for physicians on breaking medical news at [www.medpagetoday.com](http://www.medpagetoday.com)*

Clinical trial data belong to the drug companies, said Gregory Curfman, executive editor of the publication.

"We are living in the real world here," he said. "They own it. It's their data."

He defended his journal's decision to publish the finding that Multaq reduced cardiovascular deaths 29%, calling it an exploratory finding, although no such wording is used in the article.

Before such a claim can be made, another clinical trial must be done, he said. He said doctors understand what the finding means.

But Campbell, of Harvard Medical School, said drug companies use such findings to increase sales of their drugs.

"Everyone has known for a long time that drug companies use publications in academic journals to stimulate off-label use (of a drug)," he said.

Campbell said it is inappropriate for academics to put their names on such studies.

Page said he and the other academic physicians were directly involved in protocol management and data analysis.

"Based on the direct involvement in design, management, analysis and manuscript preparation, it is appropriate for the steering committee to be authors on the report," he said.

#### A common practice

At the time of the Multaq study, Page worked at the University of Washington School of Medicine. He joined the University of Wisconsin in August.

Page said his work as a paid consultant to Sanofi-Aventis and other companies ended in May 2008 because he became president of a medical society that did not allow financial ties to industry.

"This partnership of physicians with industry serves the public by providing expertise and oversight in industry-sponsored trials," he said.

It is common for academic experts such as Page to sit on steering committees of drug company-funded trials.

In an interview, Page acknowledged that he and the other authors did not get the original raw data from the Multaq trial, which involved 4,628 patients with atrial fibrillation from around the world.

He did get reports of deaths that were provided in a blinded fashion, meaning that he did not know whether the person was getting Multaq or a placebo.

He said he and other members of the study's steering committee used the blinded data to make judgments.

"Furthermore, the FDA ex-

## Treating an irregular heartbeat

Atrial fibrillation is a type of irregular heartbeat that affects more than 2 million Americans.

### Normal electrical pathways

Sinus node    Atrioventricular node

Right atrium    Left atrium

Right ventricle    Left ventricle

### Abnormal electrical pathways

Atrial fibrillation involves the two upper chambers (atria) of the heart.

### Multaq

Multaq (dronedaron) was approved last year. It costs nearly \$3,500 a year.

Journal Sentinel

amined the original data and was satisfied with the conduct of the trial," Page said. "Any suggestion that the sponsor had any influence on the conduct of the trial interpretation is inaccurate."

Working on a clinical trial in which the drug-maker controls the data is not a problem if you trust that the company is going to do the right thing, Page said.

"We knew how it was analyzed," he said. "We just didn't do the analysis ourselves, and we didn't go out and hire other statisticians to do that. This was a trial sponsored by Sanofi-Aventis and they paid for the statisticians. There is a sense of trust that they won't falsify data."

FDA advisory panel members have raised questions, not about falsified data, but about how the study was conducted.

#### Data differences

Unlike the academic authors in the Multaq trial, published by the New England Journal of Medicine, the FDA got unanalyzed raw data for its later review and did its own analysis.

One FDA panel member questioned differences between the information included in the published February 2009 study and what was submitted to the FDA.

The published paper concluded that the drug reduced cardiovascular deaths when in reality that benefit was not significant under the original study design, said advisory panel member Sanjay Kaul, who also serves as director of the vascular physiology and thrombosis research laboratory at Cedars-Sinai Heart Institute.

Determining the rate of cardiovascular death was a secondary measure of the study. The main measure was a combination of two things: hospitalization for a cardiovascular reason or death. On that count, there was 24% benefit with Multaq. It was on

that basis that the drug was approved by the FDA.

Kaul said it worked like this:

The study was supposed to stop at 4,300 patients. At that number, there was not a significant benefit in reducing cardiovascular deaths.

But the study was extended beyond its planned cutoff date and an additional 328 patients were enrolled.

The expanded version of the study included five deaths among those in the placebo group and one in the Multaq group. The company and study authors determined that was enough to report a significant cardiovascular death benefit.

That's what was published in the New England Journal study.

But the FDA did not allow the claim.

"It is not proper to change the rules in the middle of the game," Kaul said.

Page declined to respond to Journal Sentinel questions about who made the decision to add additional patients. The lead author of the study, Stefan Hohnloser, a German doctor, also would not respond to those questions.

#### Some doubts

The claimed benefit of cardiovascular death reduction was not valid for another reason, Kaul said.

Cardiovascular deaths were part of a larger category of death from any cause. Because there was no significant difference in all-cause mortality on the drug or on the placebo, the claimed reduction in cardiovascular death also was not valid.

"These observations raise questions about the quality of the data and ultimately the reliability of the findings," Kaul said.

At the time of the FDA hearing, other panel members also questioned the claim.

"The cardiovascular death claim is on shaky ground," panel member William Cal-

houn, a physician with the University of Texas in Galveston, said at the March 2009 hearing.

In an interview, Kaul said Multaq was only modestly effective at best and had no clear safety benefit.

Kaul raised the questions after Sanofi-Aventis paid for a controversial lecture this year in which off-label uses for Multaq were touted by another doctor who has worked as a consultant to the company.

The lecture was posted on Afibprofessional.org, a site launched by the American College of Cardiology and the Heart Rhythm Society. UW's Page is the president of the society.

In the lecture, the doctor claims a dramatic reduction in cardiovascular deaths with Multaq.

But when the lecture initially was posted, it did not disclose that the doctor received undisclosed consultant fees in excess of \$10,000 from Sanofi-Aventis, according to the CardioBrief blog by medical writer Larry Husten.

In March, the lecture was taken down and later re-posted, this time with the financial disclosure information.

Page said he supported the creation of the website but was not aware of its content, which was managed by the staffers.

Because of concerns raised about the lecture, his society now will include written disclosures for such activities, including verbal disclosures for audio programs.

Melia, spokeswoman for Sanofi-Aventis, said the doctor's comments were his independent view.

"Sanofi-Aventis U.S. does not engage in or endorse the off-label promotion of any product, including Multaq," she said.

*John Fauber reported this story in a joint project of the Journal Sentinel and MedPage Today. MedPage Today provides a clinical perspective for physicians on breaking medical news at www.medpagetoday.com.*

# A bone of contention for doctors

Spinal fusion protein raises questions about whether physicians should do clinical trial research on products that might enrich them

By JOHN FAUBER

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In January 2002, a group of Food and Drug Administration advisers met on whether to approve a powerful new biological agent that promised to revolutionize back surgery.

The product was like nothing the burgeoning field of spinal fusion surgery had seen before. If used properly, it essentially turned whatever it touched into bone. This was a good thing if it could be confined to the tiny space between vertebrae, but potentially calamitous if it leaked out.

One of the FDA advisers at the meeting raised a concern about nine of the doctors whose research on the product had been submitted to the FDA: The doctors all had a financial stake in the product, and their test results with it were nearly twice as good as the doctors who did not have a financial interest.

The concern by the FDA advisory panel member was laughed off with a joke, according to a transcript of the hearing, and the panel ultimately deferred to Medtronic, a company that stood to get billions in sales as the maker of the product known as Infuse.

What has happened since is no laughing matter.

Since recombinant bone morphogenetic protein-2, the biological agent used in Infuse, was approved by the FDA for fusion surgery, early concerns about its widespread, unapproved use and adverse reactions in patients have materialized. Studies have warned that it can cause life-threatening swelling in the neck, form bone in unwanted locations and possibly fuel the growth of cancer cells or spark adverse immune system reactions.

The approval of Infuse followed what drug industry critics say is a familiar playbook:

First, a buzz is created about a potential new therapy. Then, research — often by doctors with financial ties to the product — is presented to the FDA for a specific use in a narrow group of people. Once the product is on the market, other uses for it are promoted in articles and presentations, often by doctors with financial ties to the company.

Now, Medtronic is back before the FDA, this time seeking approval for a different BMP-2 product for use in back surgery. Once again, concerns about cancer, immune reactions and effectiveness have been raised by a different panel of FDA advisers.

The story of BMP-2 raises questions about whether doctors should be allowed to do clinical trial research involving products that might enrich them or the company they work for. It also shows weaknesses in the FDA process for approving drugs and devices.

"I find it very alarming that so many prominent surgeons have such cozy relationships," said Richard Deyo, a professor of family medicine at Oregon Health and Science University who has done research on spine surgery. "That concerns me a lot. It colors my reading of the data."

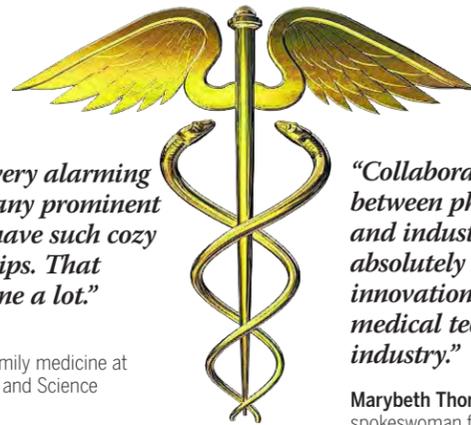
Conflicts of interest involving Thomas Zdeblick, a prominent surgeon at the University of Wisconsin-Madison, are at the heart of the BMP-2 story. He and a small group of doctors from around the country with financial ties to Medtronic have paved the way toward the product's approval and widespread use.

Zdeblick holds patent rights to a key component of the product and has received more than \$22 million dollars in royalties and other payments from Medtronic since 2002. He also is co-author of research reports about the pivotal FDA clinical trial that led to the approval of Infuse.

He declined to comment for this story. Medtronic has declined to release the names of the 60 doctors who participated in the Infuse studies and whether they had financial ties to the company.

Zdeblick is one of the doctors, but participated in a different arm of the study than the nine doctors referenced at the 2002 FDA panel hearing. However, doctors in his arm of the study who had ties to Medtronic also had better success with the product, according to FDA records.

The FDA redacted sections of its 2001 file listing the financial disclosures of the Infuse investigators, and it repeatedly told the Journal Sentinel that information no longer was available.



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Richard Deyo,  
professor of family medicine at  
Oregon Health and Science  
University

*"Collaboration between physicians and industry remains absolutely vital to innovation in the medical technology industry."*

Marybeth Thorsgaard,  
spokeswoman for Medtronic

An FDA spokesman first e-mailed this reply: "The information you are asking for was part of the sponsor's presentation and FDA did not require submission nor did the agency maintain copies."

Then Friday, a different FDA official said the agency erred and the records were available, but they would be difficult to find.

In approving the product, the FDA took into account the conflicts of interest of the investigators, said Markham Luke, chief medical officer in the FDA's device evaluation office.

Marybeth Thorsgaard, a spokeswoman for Medtronic, said the company fully disclosed the success rates of the doctors with financial ties to the company to the FDA. She noted that those doctors also had better results with the patients in the trial who did not get BMP-2.

"The panel probed the issue and made its recommendation to the FDA, which ultimately approved the product," she said in an e-mail.

She said Medtronic is strongly committed to preventing the promotion of its products for unapproved uses and has implemented corporate policies and training to prevent that.

In addition, she said the package label for BMP-2 covers all safety concerns that the FDA believes the public needs to know.

"Collaboration between physicians and industry remains absolutely vital to innovation in the medical technology industry," she added.

## Controversial treatment

Spinal fusion is a controversial treatment for degenerative disc disease with a considerable amount of evidence suggesting that many patients with back pain do just as well over time without surgery.

The expected overall success for Infuse is 57.1% — virtually the same as fusion without using BMP-2 (56.7%), the FDA noted in approving the product.

In the past, spinal fusion surgery often required harvesting a small amount of bone from the hip, which can be painful and add time to the surgery. Any new therapy that could eliminate that, such as Infuse, had blockbuster potential.

That's exactly what happened. BMP jumped from being used in less than 1% of all fusions in 2002 to being used in 25% in 2006 — much of it fueled by "off-label" use.

The FDA approved the use of BMP-2 for a single-level fusion involving the lumbar spine in which the operation was done from the front.

Since then doctors have been using it off-label in surgical approaches from the back rather than the front, and on the cervical spine as well as the lumbar spine. The cervical area is at the top of the spine, near the neck, while the lumbar area is farther down the spine, at the lower back.

One recent study found a fourfold increase in the use of all BMP products in five years, from 24,000 procedures in 2003 to 103,000 in 2007. About 85% of that was off-label use, according to the study, which was presented in March at an orthopedic surgery meeting.

While the study included a product made by a different company as well as BMP-2, the vast majority was BMP-2, said lead author Kevin Ong, managing engineer at the consulting firm Exponent Inc. of Menlo Park,



**Zdeblick**  
Millions in  
royalties

Calif.

Ong said he was surprised to see that off-label use of BMP-2 continued despite warnings about safety concerns.

#### Billions at stake

Billions of dollars were at stake eight years ago when the FDA advisory panel met to consider the fate of BMP-2.

At the time, panel member Stephen Li asked about the financially connected doctors getting better results than doctors who did not have financial ties to Medtronic.

"I don't really raise this at all to impugn anybody's integrity . . .," Li said, according to a transcript of the hearing.

Li's comment was laughed off at the hearing after he quipped about giving all doctors a financial stake in the product to improve their skill, since the ones with ties got better results.

Likewise, the panel also discounted fears that BMP-2 would be used off-label, though that concern was brought up several times at the hearing.

It is not illegal for doctors, including those with financial ties to such companies, to tout off-label use of products, although it is illegal for companies to do so. Once a drug or medical device gets FDA approval, doctors can use such products as they see fit, thereby opening up a product's potential market.

The skyrocketing off-label popularity of BMP in risky and expensive fusion surgery suggests vigorous promotion by industry-sponsored surgeons, said Eugene Carragee, a professor of orthopedic surgery at Stanford University School of Medicine.

"I don't think that any of this wasn't foreseeable from the get-go," he said.

When Infuse was approved in 2002, there was little way for the medical community and public to know if physician investigators had financial conflicts of interest, let alone how much money they got from the device companies.

Amid heightened concerns about transparency and conflicts of interest in medical research, Medtronic in May joined several drug companies in publicly listing payments to doctors — in advance of federal legislation that mandates such reporting beginning in 2013.

During the first three months of the year, about 230 physicians nationwide received payments from Medtronic of more than \$5,000 for consulting, royalties and other reasons, the company reported.

Several of the doctors on that list are the same ones who wrote articles about the original Infuse clinical trial or who wrote about off-label uses for BMP-2.

And as with Infuse, Medtronic has gone to its stable of financially connected doctors to try to sway the FDA to approve its new BMP-2 product, known as Amplify.

That research for Amplify, which targets a different slice of the lucrative spinal fusion market, was considered by the FDA last month. The Amplify clinical trial, which involved 463 patients, was completed in 2009.

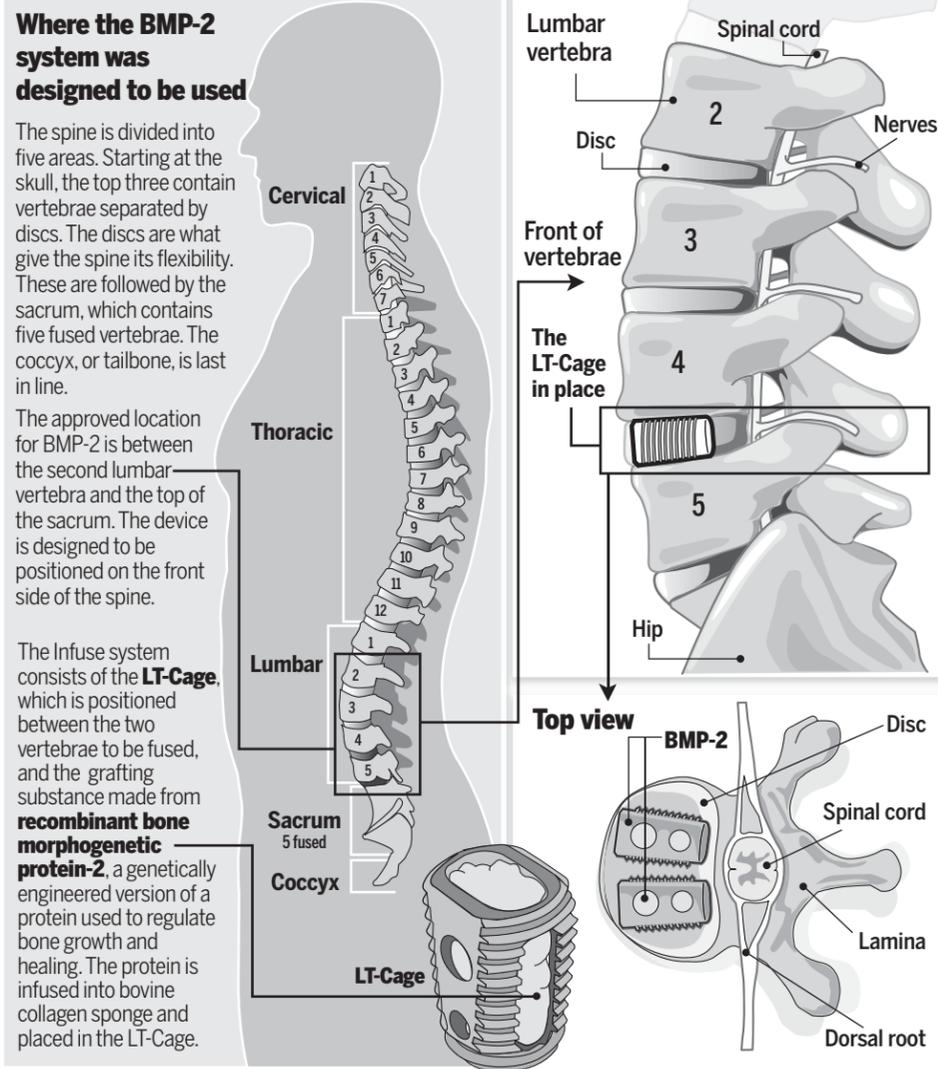
Twenty-seven of 63 surgeons — who operated on more than half of the patients in the clinical trial — had a financial interest in Medtronic at the time of the research, according to FDA records reviewed by the newspaper. Medtronic maintains that because the financially connected surgeons had results that were similar to those who did not have such conflicts, their financial interest in Amplify's success did not affect the results of the trial.

#### Infuse treatment

The Infuse treatment consists of a tapered, metallic fusion cage that looks like a thimble and the BMP-2 bone graft substitute. The substitute, which is placed inside the LT-Cage, includes the genetically engineered human

## Spine fusion device

The Infuse spinal fusion device uses a genetically engineered protein, recombinant bone morphogenetic protein-2, known as BMP-2. The product eliminates the need for a hip bone graft from the patient.



Source: Medtronic Inc.

ENRIQUE RODRIGUEZ/erodriguez@journalsentinel.com

protein (BMP-2) that is placed on an absorbable sponge.

The LT-Cage maintains spacing between the vertebrae while the BMP-2 generates the formation of new bone in order to permanently stabilize that section of the spine.

UW surgeon Zdeblick is the inventor of the LT-Cage. In 2007 alone, the LT-Cage brought him \$1.4 million in royalty payments.

Zdeblick and three other doctors co-authored a 2002 paper touting the benefits of Infuse. The paper was published in the journal that Zdeblick has been the editor of since 2002.

All four of the surgeons listed as authors show up as receiving six-figure royalty payments from Medtronic for various products during the first quarter of 2010. Zdeblick got the most among the four — \$473,000 for the three-month period.

#### Off-label concerns

The BMP-2 story highlights a problem with the way medical research is done in the United States, said Sohail Mirza, a professor of orthopedics at Dartmouth Medical School.

"The information that comes from the manufacturers and people who are very vested in the product succeeding often dominates the literature," he said. "That does taint the information. There is a conflict there."

Compelling research on the product, especially when it is used off-label, is thin, he said.

He said it is worrisome that patients may not always know that BMP-2 is being used in an unapproved approach.

"I am not sure patients always know it is off-label and I think they should," he said.

As far back as 2002, when the FDA was deciding whether to approve Infuse, experts were expressing concern that once the product was approved for one use, doctors would start using it for off-label purposes.

"After this product type is out in the marketplace if it is misused or misapplied, the potential for harm is great," Patsy Trisler, a consultant with the firm Pharmanet Inc., told the FDA advisory panel at the 2002 hearing.

One panel member, physician John Kirkpatrick, said he wanted to prevent off-label use of the product and proposed requiring that it be packaged in a way that would make that difficult. However, Medtronic officials at the hearing successfully argued against the idea.

For Medtronic, off-label use meant a potential windfall of increased sales.

Sales of BMP-2/Infuse have grown to about \$800 million a year, said Rick Wise, an analyst with the firm Leerink Swann.

He declined to estimate how much of that is from off-label use, noting that companies are not allowed to promote off-label use of their products.

"It's clear off-label use is substantial," he said.

John Fauber reported this story in a joint project of the Journal Sentinel and MedPage Today. MedPage Today provides a clinical perspective for physicians on breaking medical news at [www.medpagetoday.com](http://www.medpagetoday.com).

*"The information that comes from the manufacturers and people who are very vested in the product succeeding often dominates the literature. That does taint the information. There is a conflict there."*

Sohail Mirza, professor of orthopedics at Dartmouth Medical School

# Disjointed regulation

Pain, breakdowns mar record on jaw implants — and testing is still sketchy

By **JOHN FAUBER**  
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Before implanting a third artificial jaw joint in Heidi Clark's head, doctors had to remove particles of plastic from the second failed joint that had broken apart and become embedded in muscle.

It was the latest of five surgeries Clark has endured that have reshaped her face, damaged nerves and added to the intense pain and depression that have marked what husband Kevin calls her "long road to hell."

Like more than 10 million Americans, Clark has a condition known as temporomandibular joint disorder, or TMJ — a group of ailments affecting the joint connecting the jaw to the head.

While the disorder is often manageable and temporary, Clark first went under the knife in 1988 to be implanted with an unproven jaw joint device that had been allowed on the market by the U.S. Food and Drug Administration.

Her repeating nightmare has been experienced by thousands of others.

Since 1999, the FDA approved four jaw joint replacement devices despite weak and incomplete research clouded by potential conflicts of interest, a Journal Sentinel investigation has found. What's more, the agency approved the devices even after a disastrous series of failures and recalls during the 1980s.

The Journal Sentinel's review of several thousand pages of testimony and other documents found that the FDA ignored warnings, patient testimony and its own staff recommendations to side with device companies whose research was conducted by doctors with a financial stake in the outcome.

"There were a million red flags," said Mark Patters, who served as an FDA advisory panel member for all four of the device hearings and who voted to approve three of them between 1999 and 2002. "You don't have to know the particulars to know the science wasn't there."

The Journal Sentinel found the products were approved even though clinical trials were fraught with problems, including:

- Just two oral surgeons implanted nearly all of the devices in two of the trials.

Independent researchers say such arrangements raise red flags because clinical trials should be done at a variety of centers to get a true picture of how well a device works. When a small number of doctors implant most devices, it doesn't reflect the real-world results of surgeons with less experience with the products.

- What's more, there were financial conflicts of interest in both of those clinical trials.

In one, both doctors worked as consultants to the manufacturer, and one of them invented the device and later got royalty payments.

In the other trial, one doctor worked as a consultant to the manufacturer, helped develop the device and later received stock in the company.

- Substantial numbers of patients dropped out of all the trials, and little long-term follow-up data was available — including one trial that had data on only 34 patients at the three-year mark.

Independent doctors say this casts doubt on the findings and indicates the results may have been biased and overstated the success.

In a written response to the Journal Sentinel, the FDA stood by its approval of the devices.

Throughout the approval process, the watchdog agency appeared to be looking out more for the makers of the devices than patients, the Journal Sentinel found. Despite serious concerns, FDA advisory panels unanimously voted to approve the products in three out of four cases. With the fourth device, the advisory panel voted against approval but a higher FDA authority approved it months later anyway.

Patters, a periodontist and an associate dean at the University of Tennessee College of Dentistry, said he and other advisory members often deferred to oral surgeons on the panels who argued in closed session that the devices were needed even if poorly tested.

Financial conflicts of interest tainted all of the studies, said Christian Stohler, dean of the University of Maryland Dental School.

"There is very little science behind them," said Stohler, who serves as an adviser to the TMJ Association, a national patient advocacy group based in Brookfield.

Some doctors justify implanting the devices by saying a common problem in the jaw is best fixed by putting in a permanent device.

**BEFORE THE SURGERIES:** Heidi Clark shares a festive moment with her husband, Kevin, in 1988, before a series of failed jaw implants led to decades of pain and disfigurement.



**DAMAGE DONE:** Clark, her face swollen from surgery, embraces her daughter Marisa in 2000. Clark has temporomandibular joint disorder, and jaw implants in both sides of her face were replaced that year.

While that may work with joints such as hips, it is not always true with TMJ disorder — a poorly understood condition that can be caused by any number of factors, said Stohler.

And unlike artificial hips and knees, which often go into older people, TMJ devices typically are implanted in people in their 20s, 30s and 40s who must live with the devices for decades.

There are a few instances in which the benefits of the devices outweigh the risks — such as patients with cancer, trauma or severe rheumatoid arthritis in the joint, Stohler said. But those cases make up less than 2% of the implants installed.

Estimates suggest that over the last 20 years more than 1,000 people a year have undergone TMJ implant surgery.

"These devices should not be used in the numbers they have been used in," he said.

## Began in high school

In high school, Heidi Clark first began experiencing problems with her jaw locking.

A few years later, pain and popping in the joint sent Clark, now 47, of Colgate, to an oral surgeon. After a series of surgeries in the 1980s, her condition continued to worsen. This was before the FDA began requiring TMJ device companies to prove the safety and effectiveness of their products.

Between 1989 and 2000 she underwent a succession of radical surgeries to implant total joint replacement devices from three different companies. Her medical bills, paid mostly through insurance, totaled more than \$500,000.

The joint on her right side, made by Vitek Inc. of Houston, failed in 1991, two years after it was implanted. That device eventually was taken off the market because its materials fragmented, causing the body to attack the foreign bodies and leading to bone degeneration, permanent hearing damage and chronic pain. In some cases, bone loss in the skull from the immune system reaction actually exposed the brain.

It was replaced in 1991 with a joint made by TMJ Implants of Golden, Colo. By 1999, that joint also had failed. Plastic material from the device broke into tiny pieces that embedded in muscle tissue.

"It was everywhere," said Doran Ryan, an oral surgeon who operated on Clark in Milwaukee in 2000.

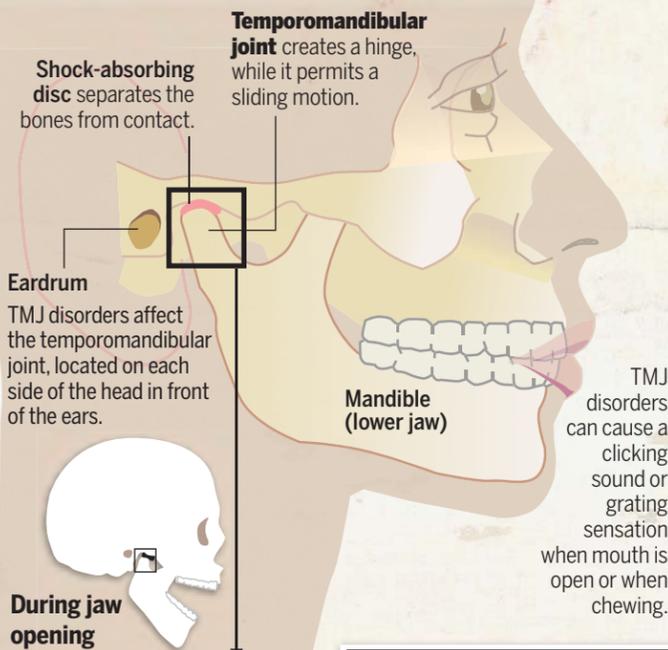
It was only in 1998 that the FDA began regulating TMJ device makers more closely.

Ryan has removed failed Vitek and TMJ Implants devices from hundreds of patients over the years.

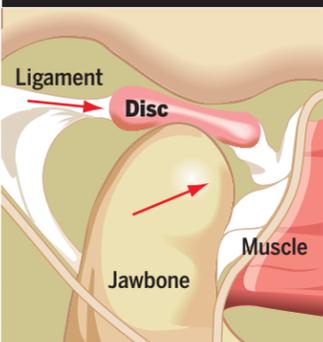
The faulty Vitek device on one side and TMJ Implants device on the other side were removed in 2000 and replaced with joints made by TMJ Concepts of Camarillo, Calif. So far, those joints have held up. That product was approved by the FDA in 1999.

# TMJ devices

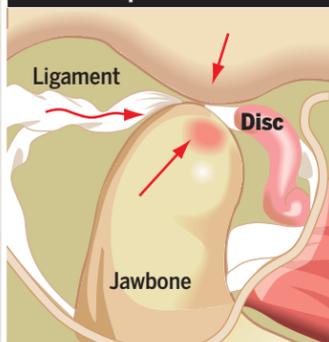
Since 1999, the FDA has approved four jaw joint replacement devices to treat temporomandibular joint disorder. Critics say clinical trial data supporting the products is weak.



**Normal: Disc prevents bones from contact**



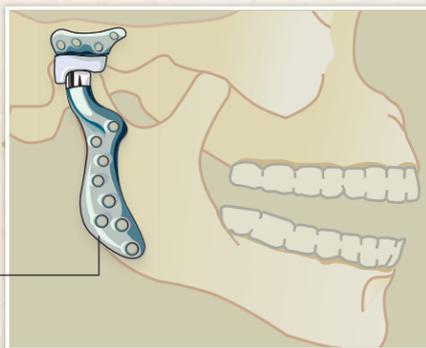
**Abnormal: Disc pulls forward, causing bone grinding and muscle displacement**



## TMJ IMPLANTS

Three companies have received FDA approval for their TMJ devices since 1999:

- TMJ Implants
- Biomet
- TMJ Concepts



## CAUSES

TMJ pain is caused by muscle spasms when chewing. Stress on the muscle groups can also be caused by grinding teeth, or a misaligned bite.

## DISORDERS CAN OCCUR IF

- Disc erodes or moves out of its proper alignment
- Arthritis damages the joint's cartilage
- The joint is damaged by impact
- The muscles that stabilize the joint become fatigued from overwork, which can happen if you habitually clench or grind your teeth

## SYMPTOMS

Signs and symptoms of TMJ disorders may include:

- Pain or tenderness of jaw
- Aching pain in and around the ear
- Difficulty in chewing or discomfort when chewing
- Aching facial pain
- Locking of the joint, making it difficult to open or close mouth
- Headache
- Uncomfortable bite
- An uneven bite, because one or more teeth are making premature contact

## SOME TREATMENTS

- Relaxation techniques
- Medication
- Mouth guards
- Surgery may be used in some cases, but only as a last resort

## THE PAINED HISTORY OF TMJ DEVICES

**1980s:** Defective TMJ devices made of Proplast-Teflon and Silastic are implanted in thousands of patients.

**1989:** The TMJ Association incorporates in Wisconsin as national advocacy group for TMJ patients.

**1991:** Vitek Inc. recalls its Proplast devices because the material fragmented, resulting in an immune response that caused bone loss, including in the skull, where the brain could be exposed.

**1992:** Congressional hearing investigates whether the Food and Drug Administration has been ignoring the dangers of TMJ implants.

**1993:** Devices made with Silastic material are removed from the market because of similar problems.

**1998:** FDA begins requiring TMJ implant companies to submit scientific data showing their products are safe and effective.

**May 10, 1999:** An FDA advisory panel raises questions about the jaw joint device made by TMJ Concepts, but recommends approval.

**May 11, 1999:** An FDA advisory panel raises questions about the jaw joint devices made by TMJ Implants, but recommends approval.

**July 1999:** FDA conditionally approves the patient-fitted prosthesis made by TMJ Concepts of Camarillo, Calif.

**October 2000:** An FDA advisory panel raises questions about the partial joint device made by TMJ Implants and recommends against approval.

**January 2001:** FDA conditionally approves the total TMJ joint prosthesis made by TMJ Implants of Golden, Colo.

**February 2001:** FDA conditionally approves the partial joint prosthesis of TMJ Implants.

**August 2002:** An FDA advisory panel raises questions about the Biomet total joint device, but recommends approval.

**2005:** FDA conditionally approves the TMJ joint replacement system of Biomet Microfixation of Jacksonville, Fla.

**2007:** GAO report raises concerns about the FDA's approval of the four TMJ devices.

**2007:** FDA wins a \$340,000 judgment against two TMJ Implants executives for failing to report 17 serious injuries related to its devices.

**2009:** A group of nine FDA scientists and reviewers writes a letter saying managers in the FDA device division are putting the public at risk by corrupting and distorting scientific evaluation of medical devices.

**September 2010:** An investment firm buys TMJ Implants out of bankruptcy and says it will continue producing its devices.

— John Fauber

Sources: Mayo Clinic, TMJ Concepts

Journal Sentinel

However, Clark's pain has not subsided. "I wake up in the morning and I feel worse until I get my medicine," she says. "Just touching it hurts so bad. I have headaches every day. I try to do things to keep my mind off it."

She takes four Vicodin a day.

It hurts to bite into food. It hurts to talk. It hurts to smile.

"I just do it," she said. "You have to smile. What is life otherwise?"

Over the last 20 years, more than 2,000 cases like Clark's have filled the files of the TMJ Association, the Brookfield organization.

One of the most appalling: A Pennsylvania woman, Margaret Rose Hutchison, underwent 60 surgeries, receiving five total joint replacement devices.

She died in 2003 at the age of 41.

Hutchison, of South Park, Pa., received her first implant at age 26, said her sister, Mary Ann Zirngibl. While the official cause of death was listed as heart-related, she had severe infections and a highly compromised immune system because of all the surgeries, Zirngibl said.

"The TMJ patients of this country deserve better," said Terrie Cowley, a patient herself and president and co-founder of the organization.

Often TMJ patients are left broke when they run out of insurance, Cowley said.

## Virtually unregulated

Many patients were victims of TMJ implant efforts that began in the 1980s and quickly became fiascos. There was virtually no regulation of the devices because of a law that grandfathered in medical devices that were "sub-

## REGULATORY PATTERN

The Food and Drug Administration's handling of TMJ devices follows a familiar pattern of the agency siding with device makers, despite concerns raised about the science they present.

In August, the Journal Sentinel reported that in 2002, the FDA approved Medtronic's BMP-2, a powerful biological agent for use in back surgery, despite evidence that doctors in that clinical trial who had financial relationships with the company got substantially better results with the product than doctors who did not have conflicts of interest. The agency redacted the financial disclosures of the doctors and declined to release them.

stantially equivalent" to products on the market before 1976.

In 1998, the FDA began requiring manufacturers to prove their devices were "safe and effective."

U.S. Sen. Herb Kohl (D-Wis.), chairman of the Senate's Special Committee on Aging, and his staff have been investigating complaints about TMJ devices.

"These devices can have benefits for some patients, but seem to have a particularly troubled history of regulation, with many people living in pain as a result," Kohl said in a statement.

The FDA declined to allow any staff members to be interviewed for this story. Instead, it provided written responses to questions about the four TMJ devices that it approved since 1999.

"TMJ patients can experience persistent pain despite treatment that includes repeated surgeries — and some chronic pain TMJ pa-

tients have no additional treatment options," The FDA response said. "After considering the totality of available information, the Agency believed that the overall assessment of risks and benefits favored approval."

The FDA also said it insisted on a carefully worded label to educate patients and practitioners, and requested that data be collected on additional patients as a condition of approval.

Even doctors associated with companies that make the devices acknowledge major flaws in the research. But they contend that approval was warranted because some patients needed the artificial joints.

"It is not scientific, but it is, unfortunately, the facts as we deal with them," said Louis Mercuri, an Illinois oral surgeon who helped develop and test one of the joint replacement devices. "We had patients who had nothing."

Though pain doesn't always improve, the devices can improve function in many patients, he said.

Critics say some patients who never should have received an implant started on a downward spiral after they did.

"These products should not be on the market unless the companies can prove that more people benefit from them than are harmed," said Diana Zuckerman, president of the National Research Center for Women & Families. "They can't do that."

Glaring deficiencies in clinical trial data presented by the three companies to the FDA was noted throughout FDA advisory panel hearings conducted between 1999 and 2002, the Journal Sentinel found in its investigation:



MICHAEL SEARS / MSEARS@JOURNALSENTINEL.COM

Heidi Clark is on hand to encourage her daughter Marisa, now 12, during riding lessons at Fox Creek Farm in Menomonee Falls. While the jaw implants Clark received in 2000 have proved durable over the past decade, during that time chronic pain has been a daily companion.

### TMJ Implants

In May 1999, TMJ Implants of Golden, Colo., went before an advisory panel seeking approval for one of its joint replacement devices.

Susan Runner, head of the FDA's dental devices branch, said there was inadequate patient data to analyze the effectiveness of the device beyond 18 months, according to a transcript of the advisory panel hearing.

She also said there were deficiencies in the company's fatigue and wear testing data.

Concerns were voiced about dozens of serious injuries associated with the company's devices.

"It is particularly of concern, I think, for a company that has been selling TMJ implants for more than 30 years, that they have yet to conduct a rigorous scientific test," panel member Patters said at the meeting.

Questions were raised about the acrylic material used in one of the products — material that later would break apart and have to be scraped out of the side of Heidi Clark's head.

Despite the concerns, the FDA approved both the TMJ Implants' partial and total joint-replacement devices.

In September, Crocker Ventures, an investment firm, bought the company out of bankruptcy and said it would continue producing the devices.

"TMJ Implants has proven to have the best implant products on the market and a solid position and reputation as a leader in the industry," Gary Crocker, president of the firm, said in a news release at the time.

Crocker Ventures did not answer questions for this story.

### Biomet

In August 2002, Peter Quinn, a University of Pennsylvania oral surgeon, and Biomet, the company he was doing research for, appeared before an FDA advisory panel, seeking approval of their total joint replacement device.

There were several problems with the research.

Of the original 180 trial cases, 132 were conducted by Quinn and 40 by Douglas Sinn, a Texas oral surgeon.

When 96% of the surgeries in a clinical trial are done by two doctors, the success of the device can be overstated because it does not reflect real-world results that less experienced surgeons are likely to have, said Charles Rosen, orthopedic surgeon and president of the Association for Medical

Ethics.

In addition, both doctors worked as consultants to the company, and Quinn was the developer of the device.

"It's two surgeons getting good results," Rosen said. "There is nothing to mitigate that conflict of interest."

Quinn told the Journal Sentinel he assigned his patent rights to the company years before the device was approved. It was only in the last year that he began getting royalty payments, he said.

He estimated he has received about \$20,000 a year as a consultant since 2002. Before that, he said, he got no more than \$25,000, and all of that he donated to his university.

Despite serious concerns about the study, the advisory panel unanimously recommended approval of the device to the FDA.

A few months later, the FDA found serious violations in the clinical trial records maintained by Sinn in Texas. Fourteen of Sinn's 41 patients had missed follow-up visits, breaking the study protocol. Forms for 14 patients left out information about adverse reactions and complications they had suffered.

The agency issued a warning letter yet approved the device anyway, despite having complete data on only 85 patients who had devices for three years, nearly all of whom got their devices from Quinn and Sinn.

There are people with pain and lost function whose joints are badly deteriorated, Quinn, senior vice president of the University of Pennsylvania Health System, said in an interview. "What do you want me to do with them? You can't say, 'Wait 15 years.'"

"This is the best data we have," he said. "I sleep very well. I would put it in a family member."

In a written response to the Journal Sentinel, Biomet said that at three years, patient satisfaction with its device was 99%. It said it has been sending reports on its study, which now includes 288 patients, up from 224 at the time of approval, to the FDA every year since the device was approved.

In addition, the company said it requires surgeons to take a course before implanting its device.

The FDA panel "thoroughly vetted" issues such as patient follow-up and bias and unanimously voted to approve the device, which helps patients with few options, Biomet spokesman Bill Kolter said in the statement.

### TMJ Concepts

When TMJ Concepts appeared before an

FDA advisory panel in 1999 seeking approval for its artificial joint device, stories of pain and suffering by patients from earlier TMJ device disasters were read into the record.

"Since these implants, I am unable to work and have a constant fever," a woman said in her letter. "Now my joints are coming out through my skin."

Another woman said: "I developed a massive lump when my first implants were put in. When I called the surgeon, he blamed me for flying in an airplane and then abandoned me."

Still another woman said, "The implants hurt so bad I cry all of the time. My surgeon told me these implants work 97% of the time."

Research on the TMJ Concepts device was marred by the high number of patients, 35%, who dropped out of the study.

Ideally, a three-year trial of a medical device should have a dropout rate of less than 6%, independent doctors say. When patients don't return, it could be a sign of dissatisfaction with the surgery's results.

TMJ Concepts researchers had lost track of so many patients that they had to rely on a subset of 111 patients for whom there was more complete data. The analysis of success over three years was based on only 34 patients, 31% of those who got the device. In addition, all 111 patients remaining had their devices implanted by Mercuri, the Illinois oral surgeon, and just one other doctor.

At the time of the panel hearing in 1999, Mercuri, then a professor of surgery at Loyola University School of Medicine in Chicago, said he had received minimal consultant's fees from the company during the previous 10 years.

However, in an interview with the Journal Sentinel, he said he started getting a stipend from the company in 2000. He also acknowledged that in 2000 he was granted stock in the manufacturer in lieu of any patent interest he might have.

In an interview, Mercuri conceded that the science behind the device was weak, but the FDA decided that something was needed to help patients.

"The only thing I can say is, the FDA thought in the case of TMJ Concepts that they had satisfied the test for safety and effectiveness," he said.

The FDA approved the device in 1999. TMJ Concepts did not comment for this story.

*John Fauber reported this story in a joint project of the Journal Sentinel and MedPage Today. MedPage Today provides a clinical perspective for physicians on breaking medical news at [www.medpagetoday.com](http://www.medpagetoday.com).*



## **JOHN FAUBER**

John Fauber has been a medical reporter at the Milwaukee Journal Sentinel since 1996. His awards include the 2010 National Headliner Award for medical/health/science writing for his ongoing "Side Effects" series on conflicts of interest at the University of Wisconsin School of Medicine; the 2010 silver Barlett & Steele Award for Investigative Business Reporting for the expanded "Side Effects" series; the 2004 Howard L. Lewis Achievement Award for a five-year collection of stories focusing on heart disease and stroke; the 2003 American Society for Microbiology's Public Communications Award for two stories he co-authored on prion diseases in humans and animals; and the 1992 Gerald Loeb Award for business and financial writing for the series "Adios Wisconsin" about Wisconsin corporations moving jobs to Mexico. He also was a finalist for the 2003 Pulitzer Prize for Explanatory Journalism for two stories he co-authored that were part of a five-part series on chronic wasting disease. As a medical reporter his primary beats are heart disease, cancer and neurology. Since 2009 much of Fauber's reporting has been devoted to the ongoing series on conflicts of interest that can compromise a doctor's judgment. Fauber has a bachelor's degree in journalism from the University of Wisconsin-Milwaukee.