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Propulsid - Lucrative Drug - Danger Signals and the FDA

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Dozens had died and more than 100 patients had suffered serious heart problems by March 1998 after taking Propulsid, a popular medicine for heartburn. Infants, given the drug to treat acid reflux, seemed particularly at risk. Federal officials told Propulsid's manufacturer, [Johnson & Johnson](#), that the drug might have to be banned for children, or even withdrawn altogether. Instead, the government and the company negotiated new warnings for the drug's label - though not nearly as tough as regulators had wanted.

Propulsid had a good year anyway. Sales continued to surpass \$1 billion. Johnson & Johnson continued to underwrite efforts that promoted Propulsid's use in children. A survey that year found that about 20 percent of babies in neonatal intensive care units were being given the drug.

Two years later, as reports of heart injuries and deaths mounted, Johnson & Johnson continued defending the safety of Propulsid, but then pulled it from the market before a government hearing threatened to draw attention to the drug's long, largely hidden, record of trouble.

That record, pieced together from newly obtained corporate and government documents, provides an in-depth view of a pharmaceutical company trying to save a lucrative drug in the face of growing evidence of harmful side effects. It is a story that has particular resonance now, as troubled arthritis painkillers - Vioxx, Celebrex and Bextra - have again focused attention on what critics say is the federal Food and Drug Administration's inability to monitor and regulate pharmaceuticals effectively once they are on the market.

Documents from lawsuits against Johnson & Johnson show that the company did not conduct safety studies urged by federal regulators and their own consultants that could have revealed Propulsid's danger early on. The F.D.A., moreover, did not disclose company research that cast doubt on Propulsid's effectiveness against digestive disorders it was being used to treat, since the studies are considered trade secrets.

Propulsid's history has striking parallels with the painkillers now at the center of controversy. Dozens of studies sponsored by Johnson & Johnson that might have warned doctors away were never published, just as the pharmaceutical manufacturer [Pfizer](#) failed to publish an early study of Celebrex that indicated a heart risk. And Johnson & Johnson was able to delay and soften some proposed label changes, just as [Merck](#) later did with Vioxx.

An F.D.A. advisory panel concluded in February that the three painkillers increased the risk of heart attacks and strokes.



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In April, Pfizer, under pressure from the F.D.A., withdrew Bextra and placed severe warnings about heart risks on the label for Celebrex, a sister pill. That followed a decision in September by Merck to withdraw Vioxx after years of insisting that it was safe.

Members of a federal advisory committee on those painkillers cited Propulsid as an example of how even the strongest warnings - known as black box warnings - do not stop physicians from prescribing a drug inappropriately.

Dr. Alastair Wood, the chairman of the panel, said in an interview that label warnings of a drug's potentially lethal effects do not protect all patients. Eventually, Johnson & Johnson made five significant changes to Propulsid's warning label and sent five letters to doctors across the country.

But Dr. Wood, an associate dean at Vanderbilt University Medical Center, said, "The case of Propulsid proves this: When people are falling off a cliff, you don't put up more signs; you put up a fence."

Despite these public warnings about Propulsid, much of the conversation between the company and regulators remained private as the drug thrived. With evidence mounting that Propulsid could interfere with the heart's electrical system, government regulators became increasingly confrontational with Johnson & Johnson executives.

But physicians were never made aware of the full depth of the agency's concerns. And even though Propulsid was never proved effective in children, the company helped finance programs that encouraged the drug's pediatric use, according to internal company documents.

Johnson & Johnson agreed last year to pay up to \$90 million to settle lawsuits that eventually involved claims that 300 people died and as many as 16,000 were injured from taking Propulsid.

Many of the documents relating to Propulsid obtained by The [New York Times](#) were filed under seal in the lawsuits.

The company declined repeated requests to make executives available to be interviewed for this article. In written responses, Johnson & Johnson defended the safety of Propulsid and said that the marketing of the pill was appropriate.

The company said it removed the drug from the market because physicians continued to prescribe it inappropriately despite repeated attempts by the company to warn them against that.

Jason Brodsky, an F.D.A. spokesman, said that the Propulsid case had been unique because doctors insisted on having access to the drug, despite its side effects, and because its label was unusually confusing. Although the F.D.A. has the power to declare a drug mislabeled



and order it off the market, it has done so only once in the last 30 years. Short of that, any label change sought by the agency has to be negotiated with manufacturers, a process that sometimes takes more than a year.

Testifying before Congress in March, Dr. Sandra Kweder, the F.D.A.'s deputy director of the office of new drugs, bemoaned such delays and said having the power to mandate label changes "would be very helpful." Even without that power from Congress, the F.D.A. has recently made moves to disclose concerns about drugs' adverse effects before label negotiations with drug makers are complete.

The government and Johnson & Johnson negotiated for five years before the company pulled Propulsid. By then, the federal government had reports of 80 heart-related deaths and 341 injuries among patients taking Propulsid.

First Signs of Trouble

The first signs of trouble emerged soon after Propulsid was approved in 1993 for the treatment of nighttime heartburn in adults. By January 1995, the F.D.A. received reports of 18 Propulsid patients who had developed serious heart arrhythmias; one patient, an infant, had died. At a private meeting that month, agency officials told Johnson & Johnson executives that the drug was causing life-threatening arrhythmias, according to F.D.A. minutes of the meeting.

Company executives insisted that such problems occurred only in patients who took Propulsid with other drugs or who had heart problems. The company sent two letters to doctors and added warnings to the drug's label listing drugs that should not be used with Propulsid.

But by July 1996, regulators had reports of 57 Propulsid patients, including seven children, who had developed serious arrhythmias or other heart problems. In August 1997, after the company told the F.D.A. that two more children taking the drug had died, a top agency official wrote to the company that Propulsid's growing number of cardiac problems among infants and children "suggests that pediatric patients may be at greater risk for them."

Johnson & Johnson had previously conducted pediatric studies of Propulsid that failed to demonstrate that the drug was effective. In January 1995, the F.D.A. told the company that without studies showing that the drug worked in children it would not receive approval for pediatric sales. Johnson & Johnson never applied for such approval and the label did not recommend it for use in children.

But doctors are free to prescribe medicines beyond the confines of labels, and Propulsid became popular among pediatricians. By 1998, doctors were writing more than half a million prescriptions a year for children and infants, according to internal company estimates. The company has said that its cherry-flavored liquid Propulsid was developed for



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geriatric patients, but company documents show that as much as 90 percent of it went to children.

Without approval for pediatric use, Johnson & Johnson could not directly promote Propulsid for children. But F.D.A. rules did allow the company to support educational efforts among doctors. A crucial player in that effort was Dr. Paul Hyman, a pediatric gastroenterologist who is now at the University of Kansas.

Dr. Hyman said in an interview that he was the first doctor in the United States, in 1984, to treat a child experimentally with Propulsid. Dr. Hyman became a Propulsid proponent. Johnson & Johnson financed some of his work and put him on its Propulsid advisory board. When he edited a textbook about childhood digestive problems that recommended Propulsid, the company paid for the press run of 10,000 copies and distributed them to doctors. In December 1997, he also made a 15-minute presentation at a Johnson & Johnson seminar where 240 doctors were trained to speak to health care professionals about the drug.

While Dr. Hyman acknowledged that Propulsid had some potentially dangerous side effects, he said they were rare. The drug was so safe, he said, that it could be used to treat "happy spitters" - infants who frequently spit up but are not ill.

"I was fairly vocal about how silly the whole death thing was, and how it was one in a million," he said.

Although the company said educational efforts were legal, Dr. Stephen B. Fredd, who oversaw Propulsid for the F.D.A., said that he had been unaware that Johnson & Johnson was supporting programs advocating the drug's use in infants.

"I had no idea they were doing anything in any way to support off-label use in pediatrics," said Dr. Fredd, former director of the F.D.A.'s gastrointestinal and coagulation drugs unit. Instead, he said, "I wanted them to warn doctors that there were dangers in using the drug."

Growing Concerns

Reports of patients who died while taking Propulsid were recorded in stark language on federal forms.

"Pathologist reports that a three-month-old female died while on Propulsid therapy," reads a July 3, 1998, report on F.D.A. MedWatch, the agency's Web site for posting potential safety problems.

Her parents reported that the child, who had undergone cardiac surgery, was sitting in her swing chair and was "fussy" at 7:50 a.m., the F.D.A. form says. "When the parents rechecked her at 8 a.m., the infant was unresponsive," it reads. "Attempts to revitalize her were futile."



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Three weeks later, the mother of an 11-week-old premature boy who had had stomach surgery and was taking Propulsid "noticed her son not breathing," another report said. Attempts were made to revive him. He was declared dead at the hospital.

Johnson & Johnson later concluded in both those cases that the patients had no risk factors that would have indicated not to use Propulsid. In a statement yesterday, Johnson & Johnson said analysis of the cases "strongly suggests" other factors may have contributed to the infants' deaths.

As injuries mounted, concern inside Johnson & Johnson about side effects among the youngest patients was growing. Johnson & Johnson researchers and executives made plans to ban sales for premature infants in the United States, an action it had taken in some European countries, according to documents obtained by The Times.

But there was internal debate. On March 16, 1998, a Johnson & Johnson regulatory affairs director, Gaetan Rouleau, sent an e-mail message to other executives saying that Propulsid could be used for premature babies and that further discussion of its use in them be delayed until after an F.D.A. meeting that month on the drug's safety.

Dirk Reyn, a Johnson & Johnson executive, wrote back to support the decision to ban Propulsid for premature babies, saying, "We do have cases and there is a scientific rationale for this."

Mr. Rouleau, however, responded that if the company agreed to ban Propulsid in premature children, it might be forced to stop selling its cherry-flavored liquid form of the drug. Unless Johnson & Johnson could justify the use of Propulsid in premature babies, he wrote, "We have very little to support the use of the suspension in children at this time."

Ultimately, the drug was not banned for premature babies. In the March 1998 meeting between the F.D.A. and company representatives, regulators expressed increasing concern about Propulsid's risks. During a presentation, an F.D.A. official projected a slide that asked, "Is it acceptable for your nighttime heartburn medicine (i.e., something for which you could take Tums) to have the potential to kill you?"

Johnson & Johnson's minutes of the meeting stated: "In F.D.A.'s opinion, cisapride is only minimally efficacious therefore no safety risk is acceptable."

In May 1998, the F.D.A. proposed major changes to the label, including adding a paragraph stating, "Despite more than 20 clinical trials in pediatric patients, safety and effectiveness of cisapride (Propulsid) have not been demonstrated in pediatric patients for any indication."

An internal company memo examined 15 of the proposed label changes and estimated that they would cost over \$250 million a year in lost sales.



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Since federal regulators cannot order changes to labels, the F.D.A. and the company negotiated. In the end, 13 of the 15 major proposed changes were either scrapped or softened. Instead of mentioning the results of the 20 clinical trials, the F.D.A. agreed to simply state that "safety and effectiveness in pediatric patients have not been established." The label said some pediatric patients had been injured and others had died while taking Propulsid, "although causality has not been established."

Financing Questions

Throughout the negotiations and label changes, the company kept up its support of doctors and patient groups that were promoting the drug as safe for use in children.

During the late 1980's and the 1990's, for example, Johnson & Johnson said it gave \$1 million to the American Pseudo-Obstruction and Hirschsprung's Disease Society. The society began as a support group for parents of children with rare digestive diseases for which Propulsid was a treatment.

By 1996, with financing from Johnson & Johnson, the group's focus had shifted to common childhood acid reflux. Dr. Hyman was the chief medical adviser to the group, which helped to train speakers who, over three years, made presentations to 6,000 to 8,000 pediatric doctors and nurses about the treatment of reflux, recommending Propulsid, said the group's founder, Andrea Anastas.

Ms. Anastas said the company had no influence over the group's activities. (Some details of the company's financial support of groups promoting Propulsid were reported in a 2003 documentary "MAMA/M.A.M.A.," by Nonny de la Peña.)

After the June 1998 label changes, the North American Society for Pediatric Gastroenterology Hepatology and Nutrition, a medical group for pediatric gastroenterologists, announced that it was going to study whether pediatricians should continue using Propulsid.

Johnson & Johnson sent the group a confidential report conceding that placebo-controlled studies, many of them never published by the company, failed to show it was effective in treating children for reflux disease. The company, which had begun financing the group before the study was announced, eventually donated \$450,000 to the society. The group report, released in May 1999, concluded that Propulsid "has a place in pediatric therapeutics."

Dr. Robert Shulman, a professor at the Baylor College of Medicine and the lead author of the report, said Johnson & Johnson's money had no influence on the group's conclusions, although he said that he regretted that its financial support was not disclosed in the paper.



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Asked how his group's recommendation squared with the company's admission that the drug had not been proved effective in infants and children, Dr. Shulman said his group understood acid reflux in children better. "We treat these kids every day," he said.

By January 2000, the F.D.A. had reports of 80 deaths and 341 serious heart problems in patients taking Propulsid. The agency scheduled a meeting to discuss its concerns with a panel of outside experts. This meeting, unlike the others at which Propulsid's safety record was discussed, would be public.

Preparing for the hearing, Janice Bush, a Johnson & Johnson executive, wrote a note during what a company spokesman said was a "brainstorming" session: "Do we want to stand in front of world and admit that we were never able to prove efficacy!" The words "never able" were underlined.

Three weeks before the scheduled hearing, Johnson & Johnson announced it would stop selling Propulsid in the United States. The hearing was canceled.