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Drug Makers Near Old Goal: A Legal Shield

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For years, Johnson & Johnson obscured evidence that its popular Ortho Evra birth control patch delivered much more estrogen than standard birth control pills, potentially increasing the risk of blood clots and strokes, according to internal company documents.

But because the Food and Drug Administration approved the patch, the company is arguing in court that it cannot be sued by women who claim that they were injured by the product — even though its old label inaccurately described the amount of estrogen it released.

This legal argument is called pre-emption. After decades of being dismissed by courts, the tactic now appears to be on the verge of success, lawyers for plaintiffs and drug companies say.

The Bush administration has argued strongly in favor of the doctrine, which holds that the F.D.A. is the only agency with enough expertise to regulate drug makers and that its decisions should not be second-guessed by courts. The Supreme Court is to rule on a case next term that could make pre-emption a legal standard for drug cases. The court already ruled in February that many suits against the makers of medical devices like pacemakers are pre-empted.

More than 3,000 women and their families have sued Johnson & Johnson, asserting that users of the Ortho Evra patch suffered heart attacks, strokes and, in 40 cases, death. From 2002 to 2006, the food and drug agency received reports of at least 50 deaths associated with the drug.

Documents and e-mail messages from Johnson & Johnson, made public as part of the lawsuits against the company, show that even before the drug agency approved the product in 2001, the company's own researchers found that the patch delivered far more estrogen each day than low-dose pills. When it reported the results publicly, the company reduced the numbers by 40 percent.

The F.D.A. did not warn the public of the potential risks until November 2005 — six years after the company's own study showed the high estrogen releases. At that point, the product's label was changed, and prescriptions fell 80 percent, to 187,000 by last February from 900,000 in March 2004.

Gloria Vanderham, a Johnson & Johnson spokeswoman, said the company acted responsibly.

"We have regularly disclosed data to the F.D.A., the medical community and the public in a timely manner," Ms. Vanderham said. "Ortho Evra is a safe and effective birth control option for women when used according to the labeling."

But Janet Abaray, a plaintiff's lawyer from Cincinnati, said that Johnson & Johnson took advantage of an agency overwhelmed by its many responsibilities.

"Johnson & Johnson knew that F.D.A. does not have the funding or the manpower to police drug

companies," Ms. Abaray said.

A series of independent assessments have concluded that the agency is poorly organized, scientifically deficient and short of money. In February, its commissioner, Andrew C. von Eschenbach, acknowledged that the agency faces a crisis and may not be "adequate to regulate the food and drugs of the 21st century."

The F.D.A. does not test experimental medicines but relies on drug makers to report the results of their own tests completely and honestly. Even when companies fail to follow agency rules, officials rarely seek to penalize them. "These are scientists, not cops," said David Vladeck, a professor at Georgetown Law School.

Last month, at a trial over the schizophrenia drug Zyprexa, Dr. John Gueriguian, a scientist who worked at the F.D.A. for two decades, testified that the agency did not always ask for strong warnings even if it believed a drug was risky. Companies typically oppose warnings, and the agency knows it must compromise on its requests or face years of delay, Dr. Gueriguian said.

"We at the F.D.A. know what we can obtain and we cannot obtain," Dr. Gueriguian said. "We have many, many problems, and we have a management system — what we can't obtain we will not ask."

For years, top officials at the agency acknowledged that lawsuits could aid the agency's oversight of safety issues. In the last decade, suits over Zyprexa, the withdrawn pain pill Vioxx, the withdrawn diabetes medicine Rezulin, the withdrawn heartburn medicine Propulsid and several antidepressants have shown that companies played down the risks of their medicines and failed to disclose clinical trials to the public even as they have aggressively marketed their drugs.

But now, the agency says a proliferation of lawsuits could lead to an overlapping patchwork of rules that would burden companies and might discourage patients from taking useful medicines.

The Ortho case, however, suggests that Johnson & Johnson, like other drug makers, is not always quick to tell the F.D.A. about potential problems with its medicines.

In 1996, the company told the agency it planned to develop the Ortho Evra patch in part because it would be likely to expose women to less estrogen than pills. The company suggested that the body would not break down hormones delivered via the patch as readily as the pill, so lower doses could be used to achieve contraception. And unlike the pill, which must be taken daily, the patch is changed weekly.

High doses of estrogen are known to raise the risk for blood clots that can cause heart attacks and strokes.

But a crucial trial completed in 1999 showed that the patch delivered 30 to 38 micrograms of estrogen into the bloodstream each day, according to company documents.

Because up to half of the estrogen in pills is lost in the digestive tract before it reaches the blood, the study suggested that the patch delivered an amount of estrogen that could be as high as a pill containing 76 micrograms of estrogen. In 1988, the F.D.A. banned birth control pills with more than 50 micrograms of estrogen.

But the study's author, Dr. Larry Abrams, who has since retired from Johnson & Johnson, decided to apply a "correction factor" to the results of the 1999 trial, according to documents. He claimed that the patch actually delivered about 40 percent less estrogen than the trial results showed — about 20 micrograms a

day.

Dr. Abrams made the change, according to his deposition, to adjust for the different ways the body metabolizes hormones from pills and patches. This adjustment was never part of the study protocol, a plan filed with the F.D.A..

"The judgment was made by the pharmacokeneticists at the time that in doing the calculation, it was probably appropriate to make that correction," Bob Tucker, a lawyer representing Johnson & Johnson, said in an interview Thursday. "Later on when people looked at it in a different time frame, they concluded that probably the correction shouldn't be applied." The company mentioned its decision to use the "correction factor" only once in a 435-page report filed with the F.D.A., and then only in a complex mathematical formula. When the study was published in 2002, there was no reference to the alteration.

Mr. Tucker said that the F.D.A. was aware of the "correction factor."

Clinical trials conducted before the patch was approved raised other red flags, as patients complained of breast soreness and nausea. "The side effects seem related" to high estrogen doses, one company scientist wrote in an e-mail message.

Two other studies, one conducted in 1999 and another in 2003, confirmed that the patch released more estrogen than the pill. Still, Johnson & Johnson delayed reporting those results to the food and drug agency, according to documents that have been made public in lawsuits.

After the patch was approved, the company marketed it as releasing 20 micrograms of estrogen to the blood every 24 hours, a figure it now acknowledges was inaccurate. It also acknowledges that the patch releases more estrogen than the pill but says that the estrogen released under the two methods cannot be directly compared.

The New York Times provided the drug agency with a copy of a court brief and asked whether agency medical reviewers were aware of the "correction factor."

Rita Chappelle, an F.D.A. spokeswoman, replied, "At present, we are reviewing the allegations and cannot comment further at this time."

Prescriptions for the patch grew rapidly after its introduction, reaching more than 900,000 by March 2004, according to data from Wolters Kluwer, a company that tracks prescription trends. But as the use of the patch rose, so did reports of side effects.

By 2004, after the death of Zakiya Kennedy, an 18-year-old college freshman in New York, food and drug officials had become concerned.

In November 2005, the agency announced that it had placed a warning that the patch "exposes women to higher levels of estrogen than most birth control pills."

Since then, an epidemiological study has shown that women on the patch can have as much as double the risk of blood clots than those taking pills. And prescriptions for the patch have fallen 80 percent.

Still, lawyers for Johnson & Johnson say that patients should not be allowed to sue the company because the

F.D.A. approved the patch and its label.

"F.D.A. is responsible for making those decisions," said John Winter, a lawyer for the company.

Judge David A. Katz of Federal District Court for the Northern District of Ohio is expected to rule soon on whether any of the lawsuits against Johnson & Johnson can go forward.

In the fall, the Supreme Court will hear a separate pre-emption case involving Wyeth, another drug company. Chris Seeger, a plaintiffs' lawyer who has about 125 Ortho Evra cases, said he expected the court to rule in Wyeth's favor.

"Our lawsuits are the ultimate check against the mistake made by the government, or fraud made by the companies against the government, or just an underfunded bureaucracy stretched thin," he said.

Janet Roberts contributed reporting.