Controversial Contraceptive Wins Approval From FDA Panel

The moment that an advisory committee of the Food and Drug Administration (FDA) voted unanimously last Friday to recommend the approval of Depo-Provera, a long-acting, injectable contraceptive made by the Upjohn Co., loud applause and a few hoots broke out from officials of several health organizations who testified that day in favor of the drug. But only a couple of the two dozen or so Upjohn officials present at the hearing cracked more than a tired smile. The reason: They've been there before. An earlier FDA advisory committee recommended approval of Depo-Provera in the mid-1970s as a general contraceptive in the United States—only to have the approval derailed after Congress raised questions about the drug's possible links to cervical cancer. And indeed, because of lingering questions about whether Depo-Provera increases the risk of breast cancer and osteoporosis, some prominent scientists continue to oppose the drug's approval.

According to Upjohn officials, getting the drug approved as a contraceptive in the United States amounts to tying up a loose end. "We don't expect it to have an effect on Upjohn's bottom line," says director of project management Frances Kimbell. The company markets Depo-Provera as a contraceptive in more than 90 countries and racks up about $100 million a year in sales, says Kimbell, who declined to estimate how much the drug's sales might rise if it's approved in the United States.

Not that Depo-Provera is unknown to U.S. consumers—for 20 years it's been marketed as a palliative treatment for cancer of the uterine lining, and some physicians have already been prescribing it as a contraceptive. But in the absence of FDA approval for that use, says Andrew M. Kaunitz, medical director of Family Health Services Inc., in Jacksonville, Florida, fears about liability prevent many physicians from prescribing the drug, which is a steroid that mimics the hormone progesterone and costs $120 for four annual injections. In addition, some countries, including India, refuse to sanction a drug unless it's approved by the country of origin. "The reason they want the drug approved is to legitimize it," says Depo-Provera researcher Samuel Shapiro, director of the Slone Epidemiology Unit at the Boston University School of Medicine. Meanwhile, many health officials in the United States are advocating Depo-Provera as a contraceptive choice because it prevents pregnancy in more than 99% of users and is tolerated better than oral contraceptives by some women.

What prompted Upjohn to test the regulatory waters again were the results from a case-controlled study recently conducted by the World Health Organization (WHO) on 12,759 women in Thailand, Mexico, and Kenya, 1561 of whom took the contraceptive. The study's results, which have been appearing in medical journals over the past several months, suggest that Depo-Provera doesn't increase the risk of cancers of the liver or cervix and may even protect against cancer of the uterine lining. However, its effect on breast cancer risk has proved to be more difficult to puzzle out.

The WHO research team, led by cancer researcher David B. Thomas of the Fred Hutchinson Cancer Research Center in Seattle, found an overall 21% increase in breast cancer in women who had taken Depo-Provera at the usual dose. But at the FDA hearing, Thomas pointed out that the increased risk "just missed" being statistically significant. Still, the risk seemed to be concentrated in women under the age of 34, who were more than twice as likely to develop breast cancer within 4 years of taking Depo-Provera than women who never took the drug, an increase that was statistically significant. Meanwhile, women of all ages ran the highest risk of getting breast cancer during the first 3 months of use. Those increases notwithstanding, Thomas argued that women who take Depo-Provera actually come out ahead when the contraceptive's effects on all cancer risks are tallied. He speculated that although Depo-Provera might cause 5.6 cases of breast cancer for every 100,000 women, it seems to prevent an estimated 19.2 cases of uterine cancer.

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While the advisory committee on fertility and maternal health drugs apparently bought that argument, other scientists weren't convinced. "All of these studies come up with the same red flag, and none of them is conclusive," says Judith Weisz, a reproductive biologist at the Milton S. Hershey Medical Center at Pennsylvania State University who in 1984 chaired a three-person panel, appointed by the FDA commissioner at Upjohn's request, to investigate concerns about Depo-Provera's side effects. That panel, a "public board of inquiry," wound up criticizing the lack of studies on the long-term safety of Depo-Provera and recommended that its impact on cancer risks be more clearly defined before it was reconsidered for FDA approval (*Science*, 23 November 1984, p. 950). Eight years later, Weisz says that Depo-Provera's link to breast cancer risk in young women remains so questionable that "it would be a travesty for the drug to be approved."

And Shapiro, although he agrees with the committee's recommendation, says that there's a notable lack of data on the long-term health effects of Depo-Provera. For him, the key question is: "Does 5 or more years of use during reproductive age increase the risk of breast cancer in post-reproductive women?" Previous studies, he says, failed to follow women past menopause, when most cases of breast cancer occur.

Weisz and others are also concerned about whether Depo-Provera might induce the bone-thinning of osteoporosis in some women. In a study led by Tim Cundy, a medical researcher at Auckland Hospital in New Zealand, women using Depo-Provera had a mean decrease of 7.5% of bone density in the lumbar spine, and 6.6% in the neck of the femur, which might make them more susceptible to the crush fractures of the spine and broken hips typical of postmenopausal osteoporosis. The advisory committee agreed that the risk of osteoporosis merited more study, and has recommended this and other follow-up studies, such as an investigation of Depo-Provera's effect on fetal development in women who take the drug before realizing they are pregnant.

For Weisz, one of the more troubling aspects of Depo-Provera is the lack of information about the effects of long-term use of the drug. "Upjohn's had 20 years to get this kind of data, and they haven't done it," she says. Right now, says Thomas, "it's impossible to pin down any mechanisms" about how Depo-Provera might induce breast cancer, although given the data, such as the finding that many cases occur in the first 3 months, one likely scenario might be that the drug stimulates the growth of pre-existing tumors.

Weisz and the other surviving member of the special review panel, epidemiologist Paul Stolley of the University of Maryland, expressed similar concerns over the safety of Norplant, another progesterone-like contraceptive, in a 1989 letter to Frank Young, then the FDA commissioner. But their appeal had little impact: Norplant was approved in December 1990. The trend is all too apparent, says Weisz: "Depo-Provera's going to be a poor person's Norplant, and we've shown neither the will nor the wish to know what really happens." Now Upjohn officials are holding their cheers until they see whether Weisz and her supporters prove more persuasive this time around.

–Richard Stone