



FDA's fast-track approval of Makena could backfire on KV

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In approving local drug maker KV Pharmaceutical Co.'s new prenatal drug, Makena, the Food and Drug Administration took a calculated risk — that its likely but not-yet-confirmed benefit in reducing pre-term births would outweigh any adverse reactions.

But the agency's fast-track approval could prove to be ill-conceived if post-approval studies indicate that the most serious complications associated with the drug — such as stillbirths — are found to be statistically significant, or if children born to mothers taking the drug are found to have developmental problems.

The Bridgeton-based drug maker won FDA approval last month to exclusively market a brand name version of the drug, which has been sold without approval for years. With its monopoly, KV has raised the drug's price from about \$15 an injection to \$1,500.

Makena's approval rested largely on one study, financed by the National Institutes of Health and published in 2003 by the New England Journal of Medicine. Makena is the commercial version of the drug 17P. The research found that 17P prevented pre-term births in about one-third of the women who received the injections.

Typically, the FDA requires three extensive clinical trials before approving a new drug. But since 1992, the FDA has granted accelerated approval for new cancer drugs and other potentially life-saving medications. The agency approves such drugs under the condition that the applicant can verify its clinical benefit through additional studies and wider market use.

An FDA official said the 2003 study provided enough evidence to approve Makena, even though it showed no direct clinical benefit in preventing infant mortality and disease.

"This was one of the best studies we've seen," FDA deputy director Sandra Kweder said of the government-financed research. But the same study showed higher rates of miscarriages and stillbirths in women taking the drug vs. those taking a placebo, as well as higher rates of pre-eclampsia, deficiencies of amniotic fluid, and gestational diabetes.

And others have expressed concern during the approval process. In 2006, the FDA's Reproductive Health Drugs Advisory Committee, which has no approval power, voted 21 to 0 to recommend further study "to evaluate the potential association of (the drug) with increased risk of second trimester miscarriage and stillbirth."

The panel split 13-8 in a separate vote on whether to recommend requiring additional study before FDA approval. But even some who favored accelerated approval had questions about the drug's effectiveness and safety.

"Even though I voted for it, I'm still skeptical," Dr. Jim Scott, professor and former chair of the Obstetrics and Gynecology department at the University of Utah, told the panel. "I think that premature labor and pre-term birth is such a huge and devastating problem that the potential benefits may outweigh the risks of non-approval."

Dr. Sidney Wolfe, director of the nonprofit Public Citizen's health research group, said the FDA probably should have gathered more study data before approval, especially given the history of pregnancy-related drugs found to either not produce a clinical benefit or trigger serious side effects.

"Both estrogen and progesterone have been tried forever to prevent miscarriages and to prevent pre-term births, and more often than not, it turns out they don't work," Wolfe said. "They could have had this answer before approval rather than afterwards. This (2003) study was finished eight years ago. Why the gap?"

Pregnancy-related drugs can affect both the mother and her fetus. In the early 1960s, thalidomide — a pill for morning sickness — was removed from markets in Europe because it was found to cause birth defects. Potential damage from the drug was reduced in the United States because FDA pharmacologist Frances Kelsey had blocked approval of thalidomide, saying that more studies were needed. In 1983, the FDA-approved drug Bendectine, also used to combat morning sickness, was taken off the market because of lawsuits asserting that it caused birth defects.

Makena is an artificial form of progesterone — a hormone produced naturally by a woman's body during pregnancy. But some medical experts have voiced concerns about the impact of the synthetic hormone on the offspring of mothers who took the drug.

"I'm afraid that we may be forced to use this compound for pre-term labor prevention. But yet, we don't know what the downstream side effects are," said Dr. Jim Liu, a reproductive endocrinologist, who voted in 2006 to recommend approval of the drug without additional studies.

Some drugs approved without extensive clinical trials have been withdrawn from the market because post-marketing studies fail to confirm a clinical benefit, or because a drug's complications outweigh its benefits. The FDA-approved pain pill Vioxx, for example, was taken off the market in 2005 because it was found to double the risk of heart attacks and strokes. According to the FDA, as many as 55,000 patients may have died from heart attacks and strokes induced by the drug.

KV Pharmaceutical — which plans to begin selling Makena on Monday — has agreed to conduct two post-marketing studies. One includes hundreds of pregnant patients in six countries and aims to determine if the drug reduces the rate of pre-term births, along with rates of infant mortality and disease in premature babies. KV's second study — to be completed in 2018, after the company's seven-year run of market exclusivity expires — will attempt to confirm initial findings that children whose mothers took Makena reach appropriate developmental targets through the age of 5.

But the FDA is "underfunded and unable to make sure that post-marketing studies get done," said Efthimios Parasidis, an assistant professor and FDA expert at St. Louis University Law School.

The way the FDA gets financed, Parasidis said, the agency's drug division gets much of its money from application fees paid by drug companies. And the companies have persuaded Congress to require the agency to spend almost all of the money to accelerate the approval process.

That leaves little left over to enforce conditions placed on drug approvals, including post-approval studies. Indeed, he said, research has shown that drug companies never complete the majority of post-approval studies.