

Studies of the emergency contraceptive in thousands of women have failed to assuage the concerns of abortion opponents and top drug regulators in the United States. Researchers see ideology trumping sound science

Plan B: A Collision of Science and Politics

The U.S. Food and Drug Administration (FDA) promised a decision on the emergency contraceptive Plan B early last summer. But on 26 August, after more than 2 years of deliberation, leaked memos, and a contentious advisory committee meeting, FDA ducked, putting off indefinitely a ruling on the application from Barr Laboratories in Woodcliff Lake, New Jersey, to move Plan B over the counter (OTC). The problem, agency officials said, was a dearth of information on whether the drug, approved for prescription use in 1999 and widely available in European pharmacies, would negatively influence the sexual behavior or health of adolescents. FDA was unsure how to restrict the drug's OTC status to older age groups.

That announcement, say critics of the non-decision, highlighted Plan B as the latest scientific issue—after climate change and evolution—to be taken ideological hostage by the Bush Administration. In late August, the head of FDA's Office of Women's Health, Susan Wood, resigned and publicly stated her disagreement with the Plan B decision. On 22 September, a *New England Journal of Medicine* editorial written by the journal's editor and two members of the two FDA advisory committees that voted in favor of the shift, citing the drug's safety, proclaimed that FDA's recent actions "have made a mockery of the process of evaluating scientific evidence."

Considered dead after the August announcement by then-FDA commissioner Lester Crawford, Plan B may yet rise again. Senators Hillary Clinton (D-NY) and Patty Murray (D-WA) had voted to confirm Crawford in July only after he promised a quick

decision on Plan B. Crawford failed to deliver. Two weeks ago, he resigned suddenly, and National Cancer Institute Director Andrew von Eschenbach was named FDA acting director (*Science*, 30 September, p. 2142). But a spokesperson for Murray says she would consider blocking the nomination of a new FDA head until the agency rules definitively on Plan B. Clinton, says a spokesperson, continues to press for a decision.

The furor stands in sharp contrast to how the issue has been handled in the rest of the world. Emergency contraception is available OTC or from a pharmacist in 39 countries. In France, it's provided by school nurses in every senior and junior high school, says James Trussell, director of the office of population research at Princeton University in New Jersey.

U.S. contraceptive researchers say the delay is inexplicable because of studies, some done years ago, that answered questions now being raised by Plan B opponents. Those studies involved thousands of young women from Scotland to San Francisco who were offered easy or more burdensome access to emergency contraception; it must be taken within 72 to 120 hours of intercourse to prevent pregnancy. They had been tested for sexually transmitted diseases and pregnancies. They'd been quizzed to determine whether keeping shrink-wrapped packs of Plan B in their nightstands made them likelier to engage in unprotected sex.

The results were unambiguous: Teenagers appeared to have no trouble understanding how to use Plan B, and its availability didn't change their behavior. Those results contributed to the near-unanimity among FDA

scientists and the scientific community that the drug ought to move from prescription-only status to OTC.

Plan B, or levonorgestrel, is a progestin-only pill that interferes with ovulation and perhaps with fertilization, explains Margaret Blythe, a pediatrician at Indiana University Medical Center in Indianapolis. Its effectiveness declines with time, which argues for making it rapidly available, say OTC supporters. Blythe spent 18 months reviewing studies of Plan B and helping write a statement for the American Academy of Pediatrics in support of OTC use. In her experience, politicians and the public often don't distinguish between Plan B and RU-486, a drug that chemically induces an abortion in the early weeks of pregnancy. Still, the difference between the two is often insufficient to appease opponents of abortion, including doctors. "We've had some physicians in the academy ... who are very, very upset" with its Plan B position, she says.

Two FDA advisory committees—on Reproductive Health Drugs and Nonprescription Drugs—together considered Barr's application in December 2003. Most members agreed that it met the OTC criteria. First, says Alastair Wood, an associate dean at Vanderbilt University in Nashville, Tennessee, and an advisory committee member who voted in favor of Barr's application, the drug is designed for an event (unprotected intercourse) that a patient can easily diagnose. Second, Plan B doesn't come with undue monitoring requirements, such as regular blood tests. And finally, side effects are few and can normally be managed without help from a doctor. The advisory committees voted unanimously that the drug was safe for OTC use.

This view is bolstered by a general belief among physicians that reproductive drugs work similarly in teenagers and adults. In the 1990s, oral contraceptive makers inquired at FDA about receiving "pediatric exclusivity": patent extensions on their products as a reward for conducting trials in a pediatric population. FDA turned down the request, says Lisa



Default strategy. If taken within a few days of unprotected sex, Plan B can prevent pregnancy.



Rarick, who spent 15 years at the agency, including as head of its reproductive drugs division, before leaving in 2003. “Reproductive-age women are reproductive-age women,” says Rarick. “The contraceptive drugs work the same in a 14-year-old [as in] a 20-year-old.” But now, with Plan B, she says, FDA is “saying kids are different.”

Opponents, including advisory committee members David Hager, an obstetrician-gynecologist at the University of Kentucky in Lexington, and Louis Cantilena, a clinical pharmacologist at the Uniformed Services University of the Health Sciences in Bethesda, Maryland, worry about how the drug might affect a teenager’s behavior. Will easier access to Plan B make teenagers more likely to engage in risky sexual behavior, and will they use the drug properly? Hager worries too about the safety of repeated use. “What happens when a young woman uses a medication three to four times a month for several months?” asks Hager of Plan B. “We just don’t know how it will affect her.” It’s true that such repetitive-use data are lacking, mainly because young women in virtually all the studies chose not to take emergency contraception very often, even if supplied it in advance.

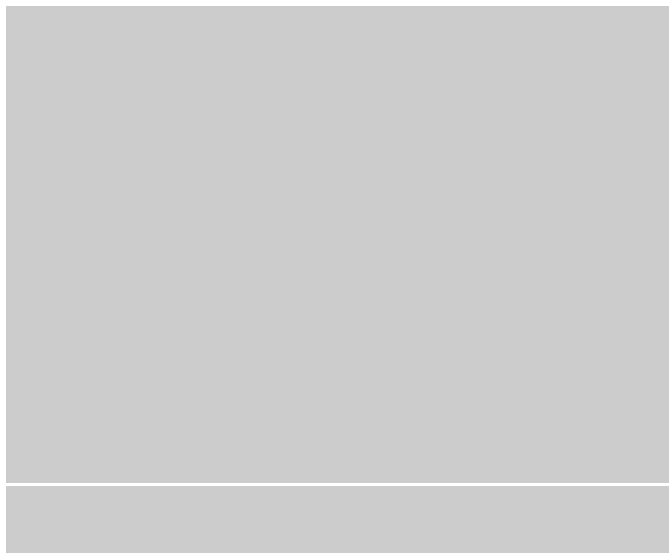
Cynthia Harper, a demographer at the University of California, San Francisco (UCSF), had some of the same questions. So in the late 1990s, she teamed up with UCSF ob-gyn Tina Raine, who runs a young women’s reproductive health clinic in San Francisco’s gritty Mission district, to follow up on a 1998 Scottish study of Plan B. That study of 1083 women (248 of them under age 20) found no difference in behavior among those offered easy access to emergency contraceptives and those who had to visit a doctor to get it. But Raine’s patients were poorer than those in the Scottish study, and at much higher risk of pregnancy. Would the results be the same?

The answer seems to be yes. In 2001, Raine and Harper began recruiting 2117 women aged 15 to 24 to follow up on a smaller pilot study they’d published in 2000. The large study, published last January in the *Journal of the American Medical Association (JAMA)*, assigned the young women to one of three groups: “advance provision” (receiving Plan B to keep at home), access to Plan B through a pharmacist, or access through a clinic.

The team found no differences in contraceptive use among the three. A similar outcome has been reported in other studies, including one of 15- to 20-year-olds in Pitts-

burgh, Pennsylvania. After 6 months, more than a third of women in the advance-provision group had used Plan B at least once, compared to a fifth of the controls. All three had similar rates of unprotected intercourse and sexually transmitted diseases. Oddly, however, despite more frequent use of Plan B among the advance-provision group, all three had similar pregnancy rates.

The comparable pregnancy figures—precisely what Plan B is designed to prevent—troubled some physicians. “Promoting easier access because it increases the use of a medication without any improvement in its desired outcome seems counterintuitive,” wrote family physician Stephen Wilson of the University of Pittsburgh Medical Center



St. Margaret Hospital and his former colleague Allen Last in a letter to *JAMA*.

The problem, Raine suspects, is that the drug was underused. “Only half the women who said they had unprotected sex” used Plan B in the *JAMA* study, she says. “Everyone’s worried that people are going to abuse it. The problem to me is that people don’t understand how easy it is to get pregnant.” Other emergency contraceptive studies have consistently found similar pregnancy rates regardless of the ease of Plan B access.

Why this is so is unclear, says Anna Glasier, an ob-gyn at the University of Edinburgh, U.K., who conducted the 1998 study as well as another on 18,000 women published last fall. She agrees that many women may not realize they’re at risk for pregnancy. Another possibility, she says, is that even at its best the drug works less well than thought, reducing the risk of pregnancy by perhaps 50% instead of 80% or more, as many believe. Still, says Glasier, who supports easy access to Plan B, “even if something is only 50% effective, it’s 100% better than doing nothing.”

David Grimes, an ob-gyn at Family Health International in Research Triangle Park, North

Carolina, distinguishes between the population effect seen in these studies and an individual woman’s need for Plan B access—“for example, a rape victim, or a woman who’s had sex with a man she does not wish to father a child with,” he says.

By 2004, the American Academy of Pediatrics, the Society for Adolescent Medicine, and the American College of Obstetricians and Gynecologists had all expressed their support for making Plan B available OTC. But at FDA, which had been reviewing data sometimes even before it was published, the effort to switch Plan B to OTC status “fell apart for nonscientific reasons,” says Grimes. “Everybody’s on board with this,” he says. “Everybody but the FDA.”

It’s unclear who made the decision to indefinitely postpone a ruling on Plan B. An internal memo in April 2004, from John Jenkins, head of FDA’s Office of New Drugs, notes that “both [FDA] divisions and offices responsible for this application have recommended approval.” Jenkins concurred with that assessment and added his own support for Barr’s application. Although FDA occasionally overrules its advisory committees—which in this case voted 23–4 in favor of OTC status—former FDA officials and those familiar with the agency say it almost never rejects the consensus of its own staff.

The FDA official who signed off on the delay—Steven Galson, head of the Center for Drug Evaluation and Research—declined through the press office to be interviewed. Susan Wood, who quit over Plan B last month, says she spoke with people below and above Galson prior to the August announcement, and “no one seemed to know what the answer was going to be. . . . The scientific staff were shut out of this decision,” including members of the commissioner’s office and the reviewing staff. Hager says that he was encouraged by someone at FDA to “write a minority opinion” on Plan B, which was submitted to the commissioner’s office. He declines to reveal who made the suggestion.

“I have never seen anything like this happen before,” says Rarick, now a consultant, who oversaw approval of both Plan B and RU-486 for prescription use. At the time, she says, FDA scientists were shielded from the politics of drug approval. “You had a buffer zone,” she says, which has since disappeared.

Now the question may be whether von Eschenbach will make a decision. “This will be [his] first test,” says Wood, “as to whether he can be independent and . . . can ensure that science drives the decision.”

—JENNIFER COUZIN