Panel Says Depo-Provera Not Proved Safe

A special panel advises FDA not to approve the drug as a general contraceptive, dealing Upjohn a severe blow.

During the past decade, the World Health Organization (WHO) and 70 foreign governments have decided that the injectable contraceptive Depo-Provera is safe enough for broad use. This determination rests largely on animal and human data drawn from more than 40 studies accumulated by the drug's manufacturer, the Upjohn Company. Recently, however, a special panel—formed by the Food and Drug Administration (FDA) at Upjohn's own request—has cast doubts on the value of many of these studies and has dealt the company a severe blow. After scrutinizing the data for 2 years, the panel last month concluded that the safety of Depo-Provera remains unproved and recommended that FDA not approve the drug for widespread use in the United States.

The panel took issue with almost every major argument that Upjohn and others have put forward in defense of Depo-Provera. If FDA commissioner Frank Young adopts the panel's recommendation that the drug should not be approved, the decision will have international repercussions. U.S. approval is key to the company's desire to expand Depo-Provera's international market. The State Department's Agency for International Development does not buy or fund the purchase of drugs for use overseas that are not approved by FDA, and some countries, such as India, do not sanction drugs that are unapproved in the country of origin. Upjohn plans to appeal the report's findings this month. "We are sorely disappointed in the report," said Upjohn president Lawrence Hoff in a statement.

Depo-Provera has long vexed FDA with political and scientific problems. Population control groups have pressed the agency to approve the drug because of its undisputed effectiveness and the need for additional birth control methods in Third World countries. A single injection of Depo-Provera can stop ovulation for 3 months and the short-term side effects are regarded as minor.

Against this backdrop, FDA has reviewed over and over again the nagging questions about Depo-Provera's long-term safety. In 1974, the FDA approved limited use of the drug. A month and a half later, after a congressional inquiry examined allegations that Depo-Provera was associated with cervical cancer, the agency stayed its order. Then, in 1978, the agency decided not to approve the drug as a contraceptive for general use in the United States, and Upjohn asked that the special panel be established. The members, who were appointed by Arthur Hull Hayes, Jr., while he was FDA commissioner, were Judith Weisz, who chaired the panel and is a professor at Pennsylvania State University and head of the reproduction biology division at Hershey Medical Center; Paul D. Stolley, professor at the University of Pennsylvania medical school; and Griff T. Ross, associate dean of clinical affairs at the University of Texas at Houston.

The company was counting on a different verdict from the one the panel delivered. In a 207-page report, Weisz and Stolley concluded that despite the vast amount of data collected, the evidence was "insufficient and inadequate" to determine the drug's potential carcinogenicity. Ross became seriously ill during the final stages of the proceedings and was unable to participate in writing the report. However, he did submit a letter for the record agreeing that Depo-Provera had been proved neither safe nor unsafe. Although Upjohn hoped that, at the very least, the panel would recommend that Depo-Provera be approved for limited use, Weisz and Stolley advised FDA against even this.

> The collection of epidemiological data has been "too haphazard and uncoordinated" to assess Depo-Provera's long-term risks, the report says.

The report contained two recurring themes—that most studies in the Depo-Provera debate have not been reviewed carefully and that there has been a failure to conduct additional, better-designed animal and human studies. "There was so much chaff," said one panelist. Said another, "Our review points out how important it is to go back to the original data rather than accept a study on its reputation."

The report concluded, for example, that animal studies do suggest that Depo-Provera is a potential human carcinogen. Upjohn has sought to dismiss these studies, arguing that the animals used—beagles and rhesus monkeys—were inappropriate models to test Depo-Provera. The panel also reviewed more than 20 epidemiological studies that have examined the cancer risk of the drug, and, one by one, found that almost every study was seriously flawed. Upjohn has agreed that the studies have limitations but argues that when considered as a whole, they do not reveal any long-term risks.

The results of beagle and monkey studies in the late 1970's raised doubts that Depo-Provera was safe. In two beagle studies, which were both sponsored by Upjohn, the drug caused high incidence of breast cancer. The company does not dispute this but has argued that the beagle responds differently than women to progestogens, the active ingredient in Depo-Provera. The panel found little to support this position. The mechanisms by which progesterone and progestogens cause breast cancer in dogs "have hardly been investigated," the report said, calling it "premature" to describe the development of cancer as a unique response by the dogs.

Upjohn has also disputed the significance of a company-sponsored monkey study in which two animals treated with 50 times the human dose developed endometrial cancer. It makes several arguments: the cancers developed from a cell type not found in women, the diseased monkeys were given such high doses that the findings are irrelevant, and Depo-Provera is currently approved by FDA to treat women with endometrial cancer. (This is the only use for which the drug is approved in the United States.)

Again, the report says that the company has not substantiated its arguments. For example, the report says that no study has been carried out to test the hypothesis that the monkeys possessed a special cell type that makes them more prone to endometrial cancer even though the hypothesis is worth considering. The high doses of Depo-Provera administered to the monkeys also cannot be dismissed because high doses may "reveal events that otherwise may take a very long time to develop or require a very large number of animals to detect."

As for the use of Depo-Provera to treat endometrial cancer, the report notes that the amount administered in cancer therapy is far smaller than the contraceptive dose. Such a paradox would not be unique: estrogens are used in small amounts to treat breast cancer in women, but in larger doses can actually promote the development of this disease.

Despite the results of the animal studies, Upjohn has stressed that the wealth of studies involving women using Depo-Provera have not yet revealed any long-term health risks. It often cites the fact that 11 million women have used its product and that 100,000 women have relied on Depo-Provera for 10 years or longer. (Depo-Provera is widely used in Thailand and New Zealand.) If the drug truly had ill effects, they would be evident by now.

Says the report, "According to this view, *quantity* of data can substitute for *quality* . . . [This argument] is [not] acceptable." Without systematic study, adverse reactions are rarely obvious. The report goes on to cite major deficiencies in the 20 epidemiological studies that have been touted as showing no cancer risk. Researchers did not include enough women, especially long-term users, failed to follow users long enough to detect cancer, used controls that were inappropriate or inadequate, did not take into account a subject's particular risk for various cancers, and failed to record data systematically.

The report says that the collection of current epidemiological data has been "too haphazard and uncoordinated" to provide a way to assess the drug's potential long-term hazards. Two studies currently under way may eventually supply the needed information. David Thomas of the University of Washington is conducting a large study funded by WHO to evaluate Depo-Provera's potential cancer risk among contraceptive users in several countries, and Upjohn is also sponsoring an epidemiological study of New Zealand women who use Depo-Provera. Panel members say that both studies are well designed.

In the end, Weisz and Stolley concluded that FDA should not sanction contraceptive uses of the drug at all. Ross, however, advised the agency to approve it for women who are mentally retarded or drug addicts.

Even limited approval would probably help foreign sales. Britain, for example, has approved Depo-Provera for a narrow population of women. Upjohn, in press statements, glosses over this and simply says that Britain approved the drug. Joseph Spiedel, vice president at the Population Crisis Committee, concedes that, if FDA approves the drug for limited use, the action might give other countries "a green light. The sophistication of interpretation is not what you'd like it to be."

Weisz and Stolley noted that even without limited approval, physicians in the United States would still have the option of prescribing the drug as a contraceptive because Depo-Provera is already on the market and approved as an anticancer drug. FDA officials say that physicians may be reluctant to do this for reasons of liability, but Weisz and Stolley recommended that, as a further disincentive, doctors should be required to obtain informed consent from patients who want to use Depo-Provera as a contraceptive.

Officials at WHO and groups with strong interests in population control are watching carefully the developments on Depo-Provera. The panel report flies in the face of WHO's assessment and acceptance of the drug, which a WHO task force reaffirmed in October shortly before the review was released. The report will be evaluated at a meeting this month, according to Peter Hall, the organization's authority on Depo-Provera. Officials at the U.S. Agency for International Development continue to monitor FDA's review of the drug. Hall and others say it is unclear how foreign governments would react if FDA decides to veto approval. After FDA withdrew its approval in 1978, several countries followed suit. At the same time, some have gone ahead and approved it.

The panel said that other countries must weigh for themselves the risks and benefits of Depo-Provera. Its task was to judge the merits of the drug for use in the United States, where the incidence of cancer of the breast and uterus is higher than in Third World countries.

Before the panel began its review, FDA's Depo-Provera records measured 45 feet of shelf space. By the time the panel finished, the files expanded to 54 feet. After an exhaustive study of a tremendous amount of data, the panel determined that Depo-Provera can be considered neither safe nor unsafe. One panel member says, "In an issue where there are strongly held opinions and a lot of emotion—where the motivations are often laudable—it is even more important to have a mechanism to look at the data objectively. Policy shouldn't shape the data." Another says in frustration, "We've missed 10 years of data collection. Upjohn and others have not proved their point."—**MARJORIE SUN**

Panel Picks Apart the Studies

"If I learned one thing from our review, it is to check every document," said a member of the special panel appointed by the Food and Drug Administration to review the safety of Depo-Provera.

The panel's report detailed major flaws in numerous studies. For example, the Upjohn Company, the manufacturer of Depo-Provera, argues that studies indicate that beagles develop breast cancer by different mechanisms than women. The panel said that some of these assertions about differences are based on single studies with serious limitations. One study had "major problems with the experimental design and with the methods used. . . . The number of animals was too small and the number of measurements were too few. . . ." In another study, the data were "too scant and incomplete. . . ."

Two studies illustrate the panel's problems with the epidemiological studies. Results in 1971 from an Upjohn-sponsored study of 1,100 women in Galveston suggested that Depo-Provera was associated with cervical cancer, but the study was not designed with controls because the experiment was to evaluate the effectiveness of the drug. To date, no follow-up studies with controls has been conducted. The panel was particularly chagrined that a large Depo-Provera study conducted at Grady Hospital in Atlanta did not provide better data. In 1978, FDA conducted an audit of the Emory University–sponsored study and uncovered serious problems. According to FDA documents, 4,700 black women were tested with Depo-Provera over a period of several years, but researchers did not adhere to the protocol approved by FDA. FDA investigators said the study was poorly designed, patient records were inadequate, and researchers did not follow patients who dropped out of the study or provide long-term follow-up to assess potential cancer risk.

"We were told 'the experts say this, the experts all agree.' Our review tells me that we experts had better be careful what we say," a panel member says.—**M. S.**