Anti-Acne Drug Poses Dilemma for FDA

Because it has caused birth defects, some want Accutane off the market. But it is a remarkable treatment for a debilitating disease. Can FDA restrict who prescribes it?

THE anti-acne drug Accutane is remarkable for its intended and unintended effects. As a result, it confronts the Food and Drug Administration (FDA) with a tough regulatory problem: how can a medically valuable drug be safely marketed when its teratogenicity is comparable to thalidomide's?

The problem was illustrated forcefully by slides shown last week at an FDA advisory committee meeting. Faces of young men and women grossly disfigured and pitted by a profusion of inflamed cysts flashed up on the screen, making it understandable why patients with severe cystic acne are often suicidal. The next pictures showed an extraordinary transformation: with Accutane treatment, the patients' complexions became smooth and clear.

But other slides displayed the horrible hazards of the drug. Children of women who took Accutane during pregnancy have been born with enormous heads, an ear located on the cheek, or no ear at all. Others have suffered heart and central nervous system disorders.

At least 62 deformed babies have been born to women undergoing Accutane therapy since the drug went on the market in 1982 in the United States, according to adverse drug reports filed with the FDA. Agency epidemiologists estimate that the number is actually as high as 600, but Accutane manufacturer Hoffmann–La Roche Inc. challenges the figure. Nonetheless, Roche officials and others acknowledge that the key issue is not the number of deformed babies itself, but that the birth defects are occurring at all.

Roche says that about a dozen lawsuits related to Accutane have been filed against the company, some of which have been settled out of court. Sales of the drug last year in the United States totaled $50 million, according to the company.

Accutane, the brand name for isotretinoin, is a cousin of vitamin A that stops skin glands from producing oil that leads to the disfiguring acne. Its development has been hailed as a major breakthrough to treat severe cystic acne, which typically lasts 8 to 9 years. The main treatment of choice previously had been antibiotics or steroids, but the benefits are only temporary. With Accutane, remission is longlasting.

Yet animal studies conducted early in the development of Accutane demonstrated that the drug is a powerful teratogen. So from the day it hit the market, Accutane has carried a strong warning that it should not be used by pregnant women.

But critics, including Sidney Wolfe of the Health Research Group, a public interest organization, say that FDA and Roche should have done more to restrict its use. Wolfe points out that in clinical trials before the drug was approved, Roche required women to be screened for pregnancy. When FDA sanctioned Accutane, however, it did not stipulate that Roche include a warning on the product label that a pregnancy test be performed prior to therapy.

After a year of Accutane sales, reports of birth defects associated with the drug began filtering in, prompting the Health Research Group to petition FDA for tougher controls. In 1984, Roche added to the label a recommendation that a pregnancy test should be performed and stepped up publicity about the hazards.

But critics, including scientists from the Centers for Disease Control, say the changes still do not go far enough. FDA epidemiologists and several members of the agency's advisory committee remark that the drug, which is available through any licensed physician in the United States, continues to be prescribed for women who do not have severe cystic acne, the only condition for which the drug is intended.

A strong warning, *but not strong enough to prevent some tragic incidents.*

Officials from FDA and Roche agree that about 270,000 women in the United States between the ages of 15 and 44 have been treated with Accutane. But they dispute the incidence of the disease and the number of deformed babies born to exposed women.

In an internal memo that recently received wide publicity, FDA epidemiologists estimated that as many as 1300 babies have been born with birth defects associated with Accutane. The figure is based on the use of Accutane and information from Medicaid patients in Michigan. At the agency meeting, the FDA researchers presented revised figures, asserting that about 597 deformed babies have been born to exposed women, based on new data gathered from a group health association in Seattle. FDA epidemiologist David Graham contends that the population of women treated with Accutane is five to six times greater than the number who actually need the drug.

Roche faults the FDA figures because the Michigan data largely represents a poor, black population that skews an extrapolation of nationwide incidence of the disease and birth defects.

Other research indicates that children born to women who used Accutane during pregnancy have a 25% chance of suffering birth defects. Edward Lammer of the California Birth Defects Monitoring Program, a state agency, has prospectively tracked 65 women who became pregnant while undergoing Accutane treatment and who, for a variety of reasons, chose not to induce abortion. Thirteen of the women aborted spontaneously; 11 of the remaining 52 gave birth to babies who had at least one major birth defect. Lammer said it is too soon to tell whether the other children who appear normal so far will eventually develop problems associated with the drug.

David Erickson, chief of the birth defects and genetic diseases branch of the Centers for Disease Control, said in a interview that recently he has received many calls from men taking Accutane, who are worried about its potential effect on them. "As far as we know, it only affects a mother," Erickson says.

FDA officials are now deliberating how to tighten controls on Accutane. At the agency meeting, officials of the American Academy of Pediatrics called for a ban on the drug unless a "foolproof" method can be devised to prevent pregnancies among users. Erickson said that in his personal opinion, it "might be appropriate" to remove Accutane

from the market. Dermatologists argued vigorously to keep the drug on the market. The Health Research Group favors keeping the drug on the market, but wants more substantial controls on distribution.

At the end of the meeting, the advisory committee, whose members are predominantly dermatologists, voted against the idea of a ban and instead recommended tighter restrictions. It did not specify how the agency should accomplish this.

Several other countries, which approved Accutane for use after FDA, currently control Accutane's distribution more rigorously than the United States. In the United Kingdom, for example, only 200 dermatologists are certified to prescribe the drug, according to a letter by Adrian Ive, a British physician, to the FDA. Sweden has chosen not to sanction Accutane for general marketing and requires doctors to submit a special request to the government to prescribe it, according to FDA official Franz Rosa.

At the hearing, some participants suggested that FDA make the drug available only through Board-certified dermatologists or particular medical centers. But the agency has never before limited doctors' prescribing powers. At the hearing, FDA commissioner Frank Young questioned whether the agency actually has the legal authority to narrow the availability of the drug to certain doctors or centers.

For its part, Roche proposes to change the product label again to stipulate, for example, that the user "is reliable in understanding and carrying out instructions." The company also proposes to offer doctors standard informed consent forms for patients and pay costs for a patient to visit an obstetrician-gynecologist to rule out pregnancy and receive contraception counseling.

Public health officials are also concerned that other retinoids on the market are causing birth defects. Last year, Roche began selling Tegison, or etretinate, in the United States to treat severe psoriasis. Tegison, also a teratogen, has a half-life perhaps as long as a year. Accutane stays in the body for a week or less. Although there are no reports of birth defects in the United States, American public health officials are aware of seven cases overseas.

They also wonder whether megadoses of vitamin A are causing birth defects. Although there is no evidence to indicate that a problem exists, the relationship has not been well studied, Erickson says. Animal studies show that vitamin A is a teratogen.

Referring to Accutane, Erickson says that "we [in the medical community] were naive to think publicity and warnings would be enough. In retrospect, we should have made a fuss sooner." ■ **MARJORIE SUN**

Fresh Look at Acid Rain

On the same day that Canadian Prime Minister Brian Mulroney came to Washington to discuss trade issues and to press for acid rain controls, the newly appointed head of the U.S. acid rain research program was called before a congressional committee to answer the many criticisms of the program he inherited.

What began as a combative session ended amicably when the new executive director of the National Acid Precipitation Assessment Program (NAPAP), James R. Mahoney, agreed to "recall" the contentious executive summary of NAPAP's 1987 interim report.

There are "grounds for hope" said James Scheuer (D–NY), chairman of the subcommittee on natural resources, agriculture research, and the environment of the House Science, Space and Technology Committee, which held the hearings.

Mahoney, a Ph.D. meteorologist who for the past 5 years headed Bechtel's environmental group, took over as executive director of the interagency program in March, replacing J. Laurence Kulp, who resigned amid intense criticism last September. In a 1987 report the General Accounting Office (GAO) criticized Kulp for the program's extensive delays—the 1985 interim assessment was not released until mid-1987—for his micromanagement style, and for neglecting policy analysis, in particular, the congressionally mandated assessment of the economic impact of acid rain effects and controls.

Most of the criticism, however, has surrounded the 1987 interim assessment, the culmination of 5 years of research and $300 million (*Science*, 18 September, 1987, p. 1404). The problem was not the four-volume report but rather the 35-page executive summary, personally written by Kulp, which was widely criticized as a misleading attempt to downplay the severity of acid rain effects. Canada's environment minister Tom McMillan denounced the summary as "voodoo" science. Kulp resigned a week after the report was released.

At the hearing Mahoney was repeatedly pressed for his opinions on whether the executive summary is "fair and accurate." Mahoney conceded that the summary differs from the report in terms of "emphasis, definition, and issues covered" but added that the summary is not as far from the underlying science as some critics have portrayed it.

"Why not rewrite it?" asked Scheuer. After some haggling, Mahoney agreed to do just that; he promised to have an "updated" summary or document of some kind back before the committee by Labor Day.

"Dr. Mahoney's pledge to issue a new report is an implicit repudiation of the interim assessment," Scheuer told *Science*. "The new report will be a litmus test of whether Dr. Mahoney can restore the damaged credibility of the NAPAP program."

In terms of the final assessment, NAPAP's extensive research program will continue unchanged, said Mahoney, but plans for assessment have been revised dramatically to allow increased outside review. NAPAP will issue a "state of the science" report in summer 1989 and the final assessment, focusing on the severity and geographic scope of acid rain effects and on the usefulness of various control strategies, in fall 1990.

The report will not make policy recommendations—"that is for Congress and the executive branch," says Mahoney—but will evaluate the costs and benefits of a few plausible control scenarios. This marks a change for NAPAP, which under Kulp had pulled back from economic analysis. All methodologies will be rigorously documented and made available, Mahoney says, so that others in Congress and the executive branch can use them to evaluate additional control strategies. A detailed plan for the integrated assessment will be sent out for review within 3 or 4 months, Mahoney said, and will be released in final form in late 1988.

In another change from his predecessor, Mahoney is bringing in five new scientists specifically to direct the assessment effort, returning to an earlier model of NAPAP organization. Kulp had restructured NAPAP, abolishing the separate task group charged with managing the assessment and taking on the job himself. Moreover, Mahoney vowed to complete the assessment on time, which could be a first for NAPAP. ■ **LESLIE ROBERTS**