Thalidomide Back—Under Strict Control

THALIDOMIDE, the notoriously teratogenic agent of the 1960s, is about to become a prescribed drug. Just 17 days after an advisory committee of the Food and Drug Administration (FDA) recommended that the acting commissioner give marketing approval to thalidomide for treatment of erythema nodosum leprosum (ENL), a complication of lepromatous leprosy, FDA informed the maker that the drug would be approved.

This use has been studied since 1965. The condition is estimated to affect only a few thousand people in the United States, but when approval is granted, the door will be open for physicians to prescribe the drug as they wish. A number of uses of thalidomide are under active investigation and some have shown considerable promise. However, even apart from its teratogenic potential, the drug is not without such occasional serious adverse effects—especially with long-term use—as irreversible peripheral neuropathy.

Thalidomide is an inhibitor of the cytokine tumor necrosis factor α (TNF-α), a property that may make it useful in mediating such diseases characterized by an excess of TNF-α as human immunodeficiency virus (HIV) infection and tuberculosis. Other conditions in which thalidomide has been clinically studied include Behçet disease, lupus erythematosus, chronic graft-vs-host disease, gliomas, Sjögren syndrome, rheumatoid arthritis, and inflammatory bowel disease. The drug also seems to have antiangiogenic properties that have prompted interest in using it to treat some cancers and macular degeneration.

An investigator with Celgene Corporation, Warren, NJ, 1 of 4 US manufacturers of thalidomide, has said that he started to list the potential clinical uses and gave up when he got to 50. Overall, says the FDA, at least 1000 patients in this country are currently using thalidomide on a compassionate basis or in clinical trials. The agency has no figures but admits that there is probably also quite a bit of "under-the-counter" use.

In addition to its application for approval of thalidomide for treating ENL, Celgene is planning to apply also for marketing approval for the use of thalidomide to treat AIDS wasting syndrome, said Sol J. Barer, the company's president. "We're also studying HIV-associated chronic intractable diarrhea, graft-vs-host disease, and severe rheumatoid arthritis,"said Barer in an interview, adding that the company has an ongoing program to develop and study the effectiveness of thalidomide analogs, compounds that retain its therapeutic benefits without the attendant toxic effects. In cell assay systems some of these compounds have shown potencies more than 10 000 times that of thalidomide, reported David Stirling, PhD, a research scientist at Celgene, at a recent meeting. He said he expected that some of these compounds would be ready to enter initial clinical trials later this year.

Federal Agency Workshop

Stirling spoke at a workship held last month at the National Institutes of Health (NIH) by that agency, the FDA, and the Centers for Disease Control and Prevention (CDC). The workshop was prompted by concern about burgeoning interest in the drug as a therapeutic agent and concomitant concern about thalidomide's teratogenic properties. At the meeting, federal officials, pharmaceutical firm representatives, physicians, and interested others—including persons with thalidomide-associated birth defects—reviewed and assessed the controversial drug. They discussed its clinical potential, risks to patients, ways to prevent birth defects associated with its use, and steps needed to monitor its safety and adverse effects. The meeting was held just days after the FDA advisory committee on dermatologic and ophthalmic drugs made its recommendation on the use of thalidomide to treat ENL.

The imminent availability of thalidomide and the increasing number of promising uses for it have raised concern that its inadvertent use by pregnant women could lead to a repetition of the situation in the 1960s when approximately 10 000 limb-reduction defects and other fetal abnormalities occurred worldwide (see sidebar). Despite the belief that there is considerable clandestine use of thalidomide, none of the fetal abnormalities associated with it have been reported recently, said Cynthia A. Moore, MD, acting deputy chief of the Birth Defects and Genetic Diseases Branch of the CDC.

No one at the workshop suggested banning the drug. The consensus was that its use be adequately controlled and distribution carefully monitored, that some system of postmarketing surveillance be put in place, and that the medical profession and the public be adequately educated regarding the drug.

There is some evidence from a preliminary survey by the FDA on over-the-counter drug labels that those least aware of the teratogenic effects of thalidomide are those most at risk: persons under the age of 45 years. "We asked people to define a series of words just as if they had seen them in a dictionary, and one of them was *thalidomide*," said Louis A. Morris, PhD, chief of the FDA's Marketing Practices and Communications Branch. "We found that two thirds of those under 45 years didn't recognize the word, while those over 45 years of age at least recognized the word even if they didn't get all the details about thalidomide correct. Thalidomide rang a bell with them." Morris noted that the survey involved only 130 people, a very small sample, so, he said, "you don't want to make too much out of it. But the results are striking."

One way to prevent the occurrence of birth defects associated with thalidomide is to limit it strictly to proven uses and to patients who cannot become pregnant. This, however, would mean that much of the use of the drug would be in uncontrolled circumstances, said Janet Woodcock, MD, director of the FDA's Center for Drug Evaluation and Research.

This point was picked up by Randolph Warren, chief executive officer of Thalidomide Victims Association of Canada, London, Ontario. A thalidomide victim himself, he expressed revulsion at the prospect of the drug's reappearance. "We will never accept a world with thalidomide in it," he said; "however, we are forced to adopt a position of preferring regulated thalidomide over unrestricted access." Warren also said he believes that when thalidomide is approved, some birth defects will inevitably follow.

He was not alone. Discussing ethical issues associated with the use of thalidomide by fertile women, Norman Fost, MD, director of the Program in Medical Ethics at University Hospital, Madison, Wis, warned, "There is no system that will prevent the single birth of a child

The Drug That Changed US Pharmaceutical History

The NIH workshop opened with a review of the history of thalidomide by Frances O. Kelsey, MD, currently deputy for scientific and medical affairs in the FDA's Office of Compliance. Kelsey was an FDA medical officer reviewing thalidomide when the manufacturer, William S. Merrell Company, a division of Richardson Merrell Inc, Cincinnati, Ohio, filed an application to market the drug as a sedative in September 1960. Kelsey recently related the circumstances under which drugs were reviewed at that time and summarized the accumulation of the evidence that finally resulted in the withdrawal of the new drug application for thalidomide.

Initially there were a number of technical concerns, she said; then there were the reports of peripheral neuritis; and, finally, in the fall of 1961, came the association of the drug with cases of fetal amelia and phocomelia in Germany, where the drug was available. The new drug application was withdrawn in March 1962, and Kelsey has long been hailed for the role she played.

Thalidomide was never approved for use in the United States, but few pharmaceutical agents have had a greater impact on drug development. The passage in 1962 of the Kefauver-Harris Act, which required that drugs be shown to be not only safe but effective (the Food, Drug, and Cosmetic Act of 1938 having required only safety), was a direct result of the experience with thalidomide, as Kelsey pointed out.

In a recent interview, she said it was not uncommon at the time for a pharmaceutical firm to send samples of a new drug to 1000 or so physicians before it received FDA marketing approval, explaining its use and saying it would soon be available—as was in fact the case with thalidomide. Ironically, it was a drug that, although effective for some indications, proved unsafe for so many that brought about a change in the accepted procedure.

"The thalidomide tragedy showed up big loopholes in the testing of drugs," Kelsey said. "Some of us knew what was going on, but we never had the backing to change it before. Sooner or later there would have been another tragedy, but it just happened that it was thalidomide that got the [Kefauver-Harris] bill through at lightning speed, and that was very satisfactory to us."

"There has never been a drug that has so profoundly affected drug development around the world as has thalidomide," said Sol Barer, the chief executive officer of thalidomide manufacturer Celgene Corporation. "It altered attitudes about drug regulation, it significantly broadened FDA authority, it affected all drug development. It changed history."—C. M.

ances the interests of future children and getting reasonable access to the drug."

Ethics Over Exclusion

Noting that thalidomide has the potential to be an effective agent for a number of conditions, Gail J. Povar, MD, clinical professor of medicine and health care science at George Washington University School of Medicine, Washington, DC, addressed the problem of off-label use—an issue that cropped up repeatedly during the workshop discussions. The data presented at the meeting provide a strong incentive to approve and promote the use of the drug, Povar noted, adding, "What worries me is that there may be desperate patients who will try to go beyond the well-documented indications to more experimental applications. When you do so, the ethical requirements go up. They extend beyond the informed consent and risk-benefit assessments of standard medical political and emotional baggage that is attached to thalidomide, Povar said. Therefore, some maintain that the drug should be excluded from use by fertile women, that its teratogenic effects pose an ethical issue that makes it different from other drugs. This attitude, she said, is a mistake. "Thalidomide poses no more and no less of a challenge than any drug with substantial promise and toxicity. We are simply dealing with an agent that, like any pharmacologic agent, purchases its effects at a price. There are benefits, but there are also risks, and physicians must weigh them carefully."

In the expectation of marketing thalidomide, Celgene has drafted a plan that it hopes will prevent fetal exposure to the drug. "The goal is zero defects," said Bruce A. Williams, the firm's vice president for sales and marketing. The plan is built on experience with restrictions on such other drugs with severe adverse effects as Accutane (Hoffmann-La Roche, Corporation, East Hanover, NJ), used to treat schizophrenia. However, the plan has some unique elements, Williams said. The manufacturer will exert "a high degree of control" over distribution of the drug and, unlike the system used by Hoffmann-LaRoche to control the use of Accutane, a tracking system would be in place to ensure compliance.

The plan has yet to be finalized, but Williams said he believes it goes a long way toward solving the problem. "It's a model for the distribution of drugs that have great benefit yet significant risk. It is a response to both the need to prevent a new thalidomide tragedy and the humane need to ensure that those who need this therapy can have appropriate access to it," he said.

Essentials of the Plan

The goal is to limit risk by supporting appropriate use for serious, debilitating, life-threatening conditions for which current therapy is inadequate or unavailable. Williams described a scenario in which a patient, considering the use of thalidomide and in consultation with a physician, would agree to counseling regarding the relative risks and benefits to ensure that the risks, including the need to avoid fetal exposure, were understood. The patient would sign an informed consent document that acknowledged his or her understanding and would agree to participate in a confidential survey at the start, during, and on the completion of therapy. Patients would be warned against letting the drug be used by anyone for whom it had not been not prescribed.

Women would be counseled about contraception; the results of a pregnancy test would have to be in hand before therapy was started; and pregnancy tests would continue during the course of therapy. "This is not a contraceptive program, it's a fetal risk-exposure prevention program," Williams emphasized. A prescription would be written for only 4 weeks of therapy, and no automatic refills would be allowed.

Male patients who are prescribed the drug would be advised to use condoms if they are sexually active. "The authorities we've talked to strongly urge us to recommend the use of condoms, in part because it's good policy from the public health perspective and in part because we can't categorically rule out the risk of the drug being transmitted in the ejaculate, although when it's been looked for it has not been found," said Celgene's Barer.

One unusual recommendation the advisory committee made was that warn-

dramatic illustration of the potential consequences of misuse.

Only physicians and pharmacies that comply with the program will be able to prescribe and dispense the drug. Pharmacies filling prescriptions for thalidomide must agree to participate in a patient-tracking system that registers all patients. The information will be confidential, and women patients will be surveyed once a month, men every 3 months. The registry will enable tracking compliance with the program; the data will be independently evaluated by the Slone Epidemiology Unit at Boston University School of Medicine, which has long experience evaluating prescription drug use. "This will provide us with constant feedback on how the program is working and how we can learn from it," said Williams.—by Charles Marwick

New Focus Placed on von Willebrand Disease

FOR MANY patients, the heavy menstrual periods, frequent nosebleeds, and ease in bruising seem normal.

They likely have a sister or mother who also has heavy periods. Or a father or brother with nosebleeds or bleeding gums. "Because others in the family have it, they just think this is life," said Anne Dilley, PhD, an epidemiologist in the Hematologic Diseases Branch of the Centers for Disease Control and Prevention (CDC) in Atlanta, Ga.

Dilley is among a group of researchers, clinicians, and advocates who want to assure patients that excessive bleeding and bruising don't have to be a way of life. They're trying to focus more attention on the often unrecognized von Willebrand disease, an autosomal disorder characterized by mucous membrane bleeding.

As Dilley embarks on the last phase of the first large-scale epidemiologic study examining the prevalence of the bleeding disorder in women, the Food and Drug Administration (FDA) is considering a label change for hemophilia drugs that often are used off-label to treat severe forms of von Willebrand. At the same time, the National Hemophilia Foundation (NHF) in New York, NY, is planning a national conference on the diagnosis and treatment of von Willebrand disease, set for next March in Philadelphia, Pa.

The recent spotlight on the illness is the culmination "of several forces coming together at once," Dilley said. While women's health has attracted political attention in the 1990s, hemophilia organizations found their political voice in the 1980s through AIDS risks their members faced from contaminated clotting factors. And scientifically, she adds, "It's an interesting public health issue."

Complex Treatment Questions

Von Willebrand disease affects about 1% to 3% of the population worldwide and about 1% of people in the United States. The vast majority—about 80%—have milder type 1 disease in which they do not produce enough von Willebrand the blood vessel walls and stabilizes factor VIII in the blood. Most of the remainder have more severe type 2 disease, in which the amount of von Willebrand factor is adequate but functionally deficient (*JAMA*. 1996;275:1814-1815). Types 1 and 2 are dominant traits; a rare, severe type 3 is recessive.

Appropriate diagnostic tests for von Willebrand disease include an activated partial thromboplastin time, template bleeding time, and ristocetin cofactor, von Willebrand antigen, and factor VIII assays. Patients with type 1 disease can be treated successfully with desmopressin acetate, available in a nasal spray since 1994. It can be used at the onset of menstrual periods and prophylactically before surgery or invasive dental procedures. Treatment issues are much more complicated in patients with type 2 disease, however, because they don't benefit from desmopressin. For more than a decade, in the United States and Europe, clinicians have treated many type 2 patients with factor VIII concentrate.

But because proof of efficacy is largely anecdotal, the concentrate has never been licensed to treat von Willebrand disease, only hemophilia. Now treatment questions are coming to the forefront as some third-party payers are reluctant to pay for drugs used to treat conditions for which they aren't indicated. "No one questioned that it wasn't indicated until the cost of health care started rising. Then certain payers questioned it," said Jeanne Lusher, MD, director of the hemostasis program at Wayne State University School of Medicine in Detroit, Mich. Cost of the concentrate could approach $1000 a dose for some patients, she said.

In response to payers, clinicians, and pharmaceutical companies that make factor VIII concentrate, the FDA scheduled a daylong workshop September 26 to examine a number of concerns. "There has been an ongoing problem regarding the proper labeling and dosage of this product" for the treatment of von Willebrand disease, said Mark Weinstein,

At the moment, Weinstein said, researchers and clinicians are not certain which assay is best at determining the amount of von Willebrand factor contained in factor VIII concentrates. It varies from lot to lot of the manufactured drug because of processing steps that can alter the molecular weight of the von Willebrand factor. Weinstein said higher weight forms of the protein are believed to have greater ability to bind platelets.

The most commonly used test to determine potency of factor VIII concentrate is the ristocetin cofactor assay. "It's an acceptable method," said Anastassios Retzios, PhD, clinical project manager at Alpha Therapeutic Corporation in Los Angeles, Calif, maker of the factor VIII concentrate Alphanate. "But there are others—collagen-binding assays and antigen measurements."

However, Weinstein noted, "There is no good correlation between these assays and clinical outcome. We don't know how to follow the level of von Willebrand factor in the plasma to know what the proper dosage is."

How Common Is the Problem?

In the meantime, Dilley is trying to determine the extent of the disease in women. "We hear from the hemophilia community. They perceive this as a much larger problem than it's currently thought to be." The study she is conducting with Carolyn Drews, PhD, of the Rollins School of Public Health of Emory University in Atlanta, Ga, has surveyed physicians on how they diagnose menorrhagia and make appropriate referrals to hematologists. Analysis of those data is being completed while collection of additional findings to help develop a clinical screening tool for bleeding disorders in women is being concluded.

The epidemiologic part of the study will try to determine the prevalence of von Willebrand disease among women with menorrhagia, which is the most common symptom of the disease in women. Dilley said the findings may help to eliminate some unnecessary hysterecto-