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BODY:

In 1960, a new federal regulator who doubted the safety of a sedative used widely in Europe, Japan, and Canada kept the drug off the American market and averted a medical catastrophe. For the middle-aged and older, the word "thalidomide" still conjures up tragic images of grossly deformed babies - as many as 10,000 worldwide - born to women who took as little as a dose or two for morning sickness when they were pregnant.

Dr. Frances Kelsey, the alert investigator for the US Food and Drug Administration, today retells the thalidomide story with the dispassion of a scientist and no hint of pride, despite her legacy of opening the era of national consumer protection. Steadied by a cane and speaking in a voice that cracks with age, Kelsey, 83, says she still worries about thalidomide - she calls it a "fascinating but rather difficult drug" - as the FDA moves toward allowing its sale.

Thalidomide, remarkably, is reemerging. A known teratogen - an agent that causes birth defects - it initially is being aimed at a tiny population of carefully monitored patients who suffer a disfiguring form of leprosy.

But ethicists, epidemiologists, and patient advocates agree that even the smallest market, the best intentions, and the most extraordinary precautions can't reduce the birth-defect risk to zero. They say that thalidomide-damaged babies will be conceived and born in the United States if the drug becomes available, as is eventually expected.

What makes that prospect even more likely is that thalidomide is showing early promise in treating a host of other, far more widespread diseases, including AIDS, tuberculosis, and cancer. Among medical researchers, the anxiety at thalidomide's awesome risks is nearly drowned out by the excitement over its potential benefits and uses.

Indeed, if the old thalidomide story was a black-and-white morality play with heroes, villains, and victims, the '90s revival is more like technicolor experimental theater: It's heavily nuanced in the ethos of "acceptable levels of risk," and has a cast of AIDS activists, eager biotech companies, product-liability lawyers, consensus-seeking government regulators, and empowered interest groups, including women's health watchdogs and even some thalidomide victims.

"We'll never accept a world with thalidomide in it," said Randolph Warren, chairman of the 125-member Thalidomide Victims Association of Canada. "But how can we, of all people, suggest that others who are suffering should be denied a drug that can help?"

Warren, whose mother took two teaspoons of the drug for morning sickness, was born in 1961 with a condition called phocomelia. It left him with no legs and only four digits on each hand. Many babies died. Those who survived had terrible deformities and severe disabilities: flippers instead of arms; instead of legs, toes attached at the hip; faces lacking eyes; missing internal organs; free-floating bones.

Worldwide, people in the early 1960s reacted with shock to newspaper stories tying thalidomide to the birth defects. But it was the graphic photos of thalidomide babies that appeared in Life and other magazines that made them gasp. To make sure that memory isn't lost - or to impress it on younger people for the first time - manufacturers of the drug plan to include a photo of a thalidomide baby on product warning labels.

Warren believes the best hope for finding a safer form of thalidomide is to give those manufacturers an incentive now, by approving the drug's sale. An FDA advisory panel this month recommended issuing the first US license for thalidomide. The agency now is studying that recommendation and is expected within months to approve the thalidomide marketing application of Celgene Corp., a New Jersey biotechnology company, along with a stringent set of safety guidelines.

Once a drug is on the market, however, physicians are free to prescribe it as they please, and no one is under any illusions that thalidomide's use will be limited to leprosy. AIDS is the expected primary market and potentially a lucrative one: Some clinical data and a lot of anecdotal evidence says thalidomide works better than any other drug in healing painful and debilitating mouth and throat ulcers and in reversing the weight-loss syndrome in HIV-infected patients.

In fact, it was the risks associated with the growing availability of bootlegged thalidomide on US streets - AIDS drug-buying clubs were obtaining it from several countries in South America and in Mexico, where the drug is legal - that prompted the FDA in late 1995 to push Celgene, which held the thalidomide patent, to produce studies and data that could lead to the drug's licensing.

"With illicit distribution, the possibility of fetal exposure to thalidomide was rising," said Janet Woodcock, director of the FDA's Center for Drug Evaluation and Research. "Most women under 35 have never heard of it. Those women in the population who are most sexually active had no knowledge of it.

"It appeared to us," Woodcock said last week at a federal interagency workshop on thalidomide, "that the most prudent path would be to get thalidomide evaluated, access to it coordinated, and its distribution under control to minimize its adverse effects."

There's irony in the FDA's rehabilitation of thalidomide, since it was the close call with the drug that turned the agency into an aggressive government watchdog in the first place. In 1962, after thalidomide was banned around the world, Congress amended the federal drug-safety law and required pharmaceutical products to be proved effective and safe before they could be sold in this country. The law is still in place, and the FDA has been the aggressive gatekeeper, a role that has often put it at odds with industry groups and with critics who argue that overregulation strangles development of new drugs, and gives foreign companies a competitive edge.

Two recent and significant developments, however - one scientific, the other political - make considering thalidomide and its medical ethics far more complicated today than it was 40 years ago.

Medical research has not unlocked the mystery of how thalidomide works, but it has revealed that the drug has more important uses than being a nonaddictive sedative and sleeping pill.

That research has dramatically changed the risk-benefit calculus on thalidomide, requiring the medical community to weigh the danger of birth defects against the drug's life-saving or life-prolonging potential in patients with AIDS or cancer, or in rarer ailments such as lupus or Crohn's disease, where there are no known therapeutic alternatives.

"Thalidomide's dangers are undeniable, but it is showing to be an effective drug in places where other treatments are sorely missing the mark," said Dr. Gail Povar, a medical ethicist at George Washington University School of Medicine. "I believe there is a strong ethical justification to promote thalidomide for life-threatening illnesses, which is profoundly different from promoting it for insomnia. Doctors must accept certain levels of risk to do good."

But who defines doing good? In 1960, Kelsey and a couple of colleagues made a fateful call on thalidomide. Today, politics and competing constituencies play a much bigger role, and no decision can be made without public hearings, extensive comments, and due consideration of the concerns of every affected group, particularly patient advocates The FDA has spent more than a year building consensus and trying to avoid confrontation on thalidomide.

So far, it's working, despite the raw emotions attached to the drug. Thalidomide survivors make a compelling case for caution. AIDS activists, who have set the modern standard for patient advocacy, threaten to use any means, legal or illegal, to get it approved as a drug of last resort. Feminist groups are warning the FDA not to place any restrictions on thalidomide distribution that would prevent women of child-bearing age from obtaining it or that would deny women free choice in the kind of contraception they choose when they are taking it.

Physicians groups have weighed in, urging that the FDA not interfere with the practice of medicine by trying to control or limit how to prescribe it. Product-liability lawyers say doctors should proceed at their own risk with "off-label" prescriptions, and they predict far more legal wrangling than 40 years ago if thalidomide babies are born. "No matter how good the warnings are, there will be children born of mothers who took thalidomide, and there will be lawsuits," said Frank Woodside, a Cincinnati lawyer who has defended many pharmaceutical companies in liability suits.

The risks from the drug are high. A single dose of thalidomide, taken during the first three weeks of a pregnancy, exposes a fetus to a 50 to 90 percent risk of malformation. Recognizing such dangers, the Celgene Corp. has proposed a rigorous education and pregnancy-prevention program. That will include contraception counseling, mandatory pregnancy testing, and registration for doctors and pharmacists who write or fill thalidomide prescriptions. Patients will be required to sign consent forms and participate in surveys to measure compliance with the program and to report pregnancies.

Since 1989, Dr. Allen Mitchell of the Boston University School of Medicine has surveyed women who take Accutane, a proven teratogen, for a severe form of acne. Among 210,000 women who participated in the survey and presumably were well-informed of the risks, 632 became pregnant while taking the drug. Of those pregnancies, 11 percent resulted in live births (68 percent of the pregnancies were voluntarily aborted.) Of the babies born, between 20 and 30 percent had birth defects.

The experience with Accutane is common: Once it reached the market, the drug was prescribed far more widely than just for patients with severe symptoms. Some observers expect that thalidomide, too, will be used to treat diseases that are not life-threatening and will eventually expose many women of child-bearing age to its risks.

"I'm afraid we're on a slippery slope with thalidomide," said Dr. Cynthia Moore, deputy chief of the birth defects branch of the Centers for Disease Control and Prevention in Atlanta. "Babies with birth defects will be born, we'll be expecting it, so we won't be shocked. Still, at some point we'll have to answer this question: 'When has the risk become just too great?' "

Thalidomide's history

1956: The drug thalidomide is developed by German scientists as a sedative-hypnotic agent. It is marketed in West

Germany under the name Contergan and sold by prescription and over the counter as a sleeping pill.

1958: Marketing of thalidomide extends to more than 40 countries, including the United Kingdom, Canada, and Japan, and it is prescribed as a therapy for morning sickness in pregnant women.

1960: US Food and Drug Administration receives a "new drug" application for thalidomide. Medical investigator Dr. Frances Kelsey blocks the license and requests more information on the drug's safety and side effects.

1962: The Richardson-Merrill pharmaceutical company withdraws its application to the FDA for thalidomide after the German manufacturer pulls the drug from the market, pending investigation of reports that it is associated with phocomelia, a rare birth defect. Over time, 10,000 "thalidomide babies" are identified worldwide.

1962: Congress strengthens the 1938 Food, Drug, and Cosmetic Act to require that new drugs must be proved effective as well as safe before they rough for treating diseases such as AIDS and tuberculosis.

1994: The World Health Organization designates thalidomide as the drug of choice for treating ENL.

1994: The FDA begins an interagency thalidomide working group to assess research advances, including successful therapies in treating leprosy, as well as mouth ulcers and weight loss in HIV-infected patients, and to address the growing availability of illegal thalidomide through AIDS drug-buying clubs.

1995: The FDA requests that Celgene Corp., a biotech company with patent rights to thalidomide, step up its studies and submit an application for marketing it for leprosy patients. Celgene applies for the license in late 1996.

1997: Researchers at Boston's Children's Hospital report that thalidomide, used to slow blood-vessel activity, shows significant results in halting or reversing the growth of lethal tumors in patients with brain cancer.

1997: An FDA advisory panel recommends that the agency approve licensing thalidomide for treatment of leprosy. A decision is pending.

GRAPHIC: PHOTO

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