Health Law and Ethics

Thalidomide and the *Titanic*: Reconstructing the Technology Tragedies of the Twentieth Century

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ABSTRACT

The *Titanic* has become a metaphor for the disastrous consequences of an unqualified belief in the safety and invincibility of new technology. Similarly, the thalidomide tragedy stands for all of the "monsters" that can be inadvertently or negligently created by modern medicibne. Thalidomide, once banned, has returned to the center of controversy with the Food and Drug Administration's (FDA's) announcement that thalidomide will be placed on the market for the treatment of erythema nodosum leprosum, a severe dermatological complication of Hansen's disease. Although this indication is very restricted, thalidomide will be available for off-label uses once it is on the market.

New laws regarding abortion and a new technology, ultrasound, make reasonable the approval of thalidomide for patients who suffer from serious conditions it can alleviate. In addition, the FDA and the manufacturer have proposed the most stringent postmarketing monitoring ever used for a prescription drug, including counseling, contraception, and ultrasonography in the event of pregnancy.

The *Titanic*/thalidomide lesson for the FDA and public health is that rules and guidelines alone are not sufficient to guarantee safety. Continuous vigilance will be required to ensure that all reasonable postmarketing monitoring steps are actually taken to avoid predictable and preventable teratogenic disasters. (*Am J Public Health*. 1999; 89:98–101)

At the close of the 20th century, there seems to be a longing to make some sense of the century's most celebrated technological tragedies. The tragedies of the *Titanic* and thalidomide rank at or near the top in our pro-progress culture's consciousness of technological disasters. Each has had a much wider impact on the world than is reflected in the loss of life and limb, and each has come to stand for disaster caused by a combination of greed and overconfidence in technology.

The *Titanic*, of course, has become a metaphor for the disastrous consequences of an unqualified belief in the safety and invincibility of new technology.[1] Although only 1500 people lost their lives when the ship went down, it was the total surprise the world felt at the sinking of this "unsinkable" ship that presaged the collapse of the old order of British invincibility and technological superiority. The *Titanic* probably was the safest passenger ship of its time, but human mistakes and overreliance on technology magnified the loss of life when the ship sank. Survivor Lawrence Beesley noted, reflecting on the tragedy and how similar tragedies might be avoided in the future, "The range of the wireless apparatus might be extended, but the principal defect is the lack of an operator for night duty on some ships. The awful fact that the *California* lay a few miles away, able to save every soul on board, and could not catch the message because the operator was asleep, seems too cruel to dwell upon."[2] The *Titanic* has, of course, been symbolically raised at century's end by its celebration in the most commercially successful film in history, *Titanic,* in which the story of the ship's sinking is reconstructed for our technological age. Even when the story is reconstructed with a "love conquers all" theme, we remain fascinated with the idea that nature, whether in the form of an iceberg, a tornado, a volcano, or an asteroid, can cause harm uncontrollable by technology.

The thalidomide tragedy of midcentury is much more recent than the *Titanic* tragedy, but it already stands for all of the deformities and "monsters" that can be inadvertently or negligently created by modern medicine.[3,4] Thalidomide's harm cannot be totally controlled. Nonetheless, through a combination of careful medical postmarketing monitoring and new laws, today thalidomide can be thought of as doing more good than harm. Thalidomide also holds wider postmarketing lessons for all drugs that carry potentially devastating dangers.

Thalidomide as Teratogen

The popular medical belief that the human fetus was protected from maternal drug exposures in the *sanctum sanctorum* of the uterus[5] was shattered in 1961 when Lenz[6] in Germany and McBride[7] in Australia independently suggested that prenatal exposure to thalidomide was the cause of serious birth defects. These abnormalities came to be known as thalidomide embryopathy, which includes amelia or phocomelia, cranial nerve palsies, microtia, choanal atresia, congenital heart defects (e.g., ductus, conotruncal defects), bowel atresias, gallbladder aplasia, and urogenital abnormalities.[8] Thalidomide was first introduced in Germany in 1958 as an anticonvulsive agent but was soon found unsuitable for this indication. Nonetheless, clinicians recognized that this drug was useful for a variety of other ailments, including morning sickness caused by pregnancy,

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This paper was accepted August 14, 1998.

hypertension, and migraines.[9] In the United States, Richardson-Merrill hoped ultimately to have thalidomide approved as an over-the-counter drug and planned to recommend it as treatment for myriad problems including alcoholism, anorexia, asthma, cancer, poor schoolwork, premature ejaculation, psychasthenia, and tuberculosis.[4]

By 1961, thalidomide was widely prescribed in Europe. Pregnant women in 48 countries took thalidomide, resulting in the live births of more than 8000 affected infants.[4] Of infants exposed between days 35 and 48 after the last menstrual period, 20% to 30% had severe limb defects and other organ defects.[10,11] In the United States, the drug had failed to receive Food and Drug Administration (FDA) approval, not because of potential teratogenicity but because of concerns about peripheral neuropathy.[4] Even though Richardson-Merrill distributed more than 2.5 million thalidomide tablets to 1267 physicians who gave them to some 20 000 patients in "clinical trials," only 17 affected infants were reported in the United States.[4] Once thalidomide was withdrawn from the market worldwide, affected infants continued to be born up to about May 1963 and very exceptionally beyond this date.[4,8] The drug's legalization in Brazil and use in South America, may, however, have resulted in at least 34 cases of thalidomide embryopathy since 1965.[12] The next chapter in history's most notorious human teratogen is about to be written.

New Indications for Thalidomide

Thalidomide has returned to the center of an emotionally charged controversy. On July 16, 1998, the FDA cleared thalidomide for marketing by a New Jersey–based pharmaceutical company, Celgene, Inc, for erythema nodosum leprosum, a severe dermatological complication of Hansen's disease (formerly known as leprosy).[13] Hansen's disease affects about 7000 people in the United States, and approximately 50 of them are affected by erythema nodosum leprosum. The FDA has announced that thalidomide will be among the most tightly restricted drugs ever to be marketed in the United States.[14] The drug policy question is how strict these postmarketing approval controls should be.

Celgene, in cooperation with the FDA, has developed the System for Thalidomide Education and Prescribing Safety (STEPS) program. This program includes mandatory registration of all physicians who prescribe the medication and all patients who take it, as well as mandatory contraceptive measures for both males and females.[14] Women who take thalidomide must have a negative pregnancy test result, show proof that they are using 2 forms of contraception, and submit to monthly pregnancy tests (weekly in the first month).[14] Drawings of deformed infants must appear on every package of the drug. Both the patient and the physician must sign a document signifying that the patient understands the risks and is using contraception.[13,14] Prescriptions are limited to a 1-month supply. Whether thalidomide use in males affects sperm or fetal development is unknown, but males taking the drug will be counseled to use condoms when having intercourse with women of childbearing age.[14] Thalidomide causes not only birth defects but also peripheral neuropathy, and patients must be monitored to determine "how dose and use of the drug affects onset of this side effect and irreversibility."[14] These controls put thalidomide among the most stringently regulated drugs in the United States, but this may not be saying much.

Although thalidomide would be marketed for use in erythema nodosum leprosum, physicians would be able to prescribe it for so-called off-label uses (i.e., for other than erythema nodosum leprosum). For example, thalidomide has been shown to be effective in the treatment of oral aphthous ulcers of the mouth and oropharynx in patients with HIV infection.[15] Such ulcers can be extensive and debilitating, and thalidomide appears effective for pain relief and allows patients to eat and in some cases avoid a cachectic death. More than half of the patients with these ulcers are completely healed by 4 weeks of drug therapy, and almost 90% are at least partially healed.[15] Indeed, thalidomide appears to be so successful in oral aphthous ulcer treatment that within the last few years buyer's clubs have been purchasing the drug in Brazil, where it is legally available, and distributing it illegally to AIDS patients in the United States. Just as in the early 1960s, claims have also been made for the beneficial effects of thalidomide in many conditions, including macular degeneration, rheumatoid arthritis, diabetes mellitus, graft-vs-host disease following bone marrow transplants, autoimmune diseases, and some cancers. Thus, the off-label use of thalidomide may inevitably lead to exposure of many fetuses.

Risk-Benefit Analysis

Did the FDA properly weigh the risks and benefits of introducing thalidomide to the US market? The major risk is the inevitable tragedy that infants will again be born with the thalidomide embryopathy. Extensive regulations will be helpful but do not guarantee prevention of such births. The closest analogy is Accutane, an antiacne medication that can also cause severe birth defects.[16] The FDA tightly regulates its use. Nonetheless, up to 8 infants with isotretinoin-related malformations are born each year in the United States (A. A. Mitchell, oral communication, April 29, 1998).

Since the 1960s, a legal change and a technological development—*Roe v Wade*[17] and ultrasonography—have made thalidomide a "different" drug today. These 2 changes make it reasonable to treat thalidomide in a similar way to the other approximately 30 drugs that carry a serious risk to the fetus.[11] Since 1973 and the US Supreme Court's decision in *Roe v Wade*, American woman have had a constitutional right to terminate their pregnancies prior to fetal viability. At the time that thalidomide failed to obtain FDA approval in the United States, abortion, with a few exceptions, was a crime. The thalidomide tragedy itself had a direct role in helping to change the public's attitude toward abortion. In late 1962, Sherri Chessen Finkbine read a newspaper article linking thalidomide to birth defects and later discovered that the "headache pills" her husband had obtained on a trip to England contained thalidomide.[18] Unable to have an abortion in Arizona, she ultimately flew to Sweden for the abortion of what turned out to be an affected fetus. Her story was widely publicized, and a Gallup poll conducted soon thereafter showed that 52% of Americans thought she had done the right thing.[18] Also, the major potential effect of thalidomide on the fetus is limb deformity, which can now be observed relatively early in pregnancy by ultrasound, a technology not available in the 1960s.

Any reasonable attempt to prevent the birth of infants with physical disabilities requires counseling patients who are taking thalidomide not to become pregnant and urging those in whom contraception fails either to discontinue the drug or to agree to have their fetuses evaluated for severe structural anomalies by high-resolution ultrasonography. Most major fetal malformations can be detected by ultrasonography, at least by 18 to 20 weeks' gestation. The final abortion decision, nonetheless, must be the woman's. Women, not the government, their employers, or their physicians, must make the final decisions about continuing or not continuing their pregnancies.[19]

The most compelling benefit of FDA approval of thalidomide is that it makes thalidomide available to patients who have conditions it can alleviate. In cases in which the suffering is great, no reasonable medical

alternatives are available, and thalidomide is effective, the FDA is correct to conclude that its teratogenicity alone should not preclude its use. Women should not be denied effective therapy for severe existing disease solely because the therapy poses potentially severe risks to their fetuses. Because of thalidomide's teratogenicity, however, physicians have a responsibility not to prescribe it to fertile women unless no reasonable medical alternative exists, the condition being treated is serious, reliable contraception is used, and the woman is fully informed of the drug's risks and benefits. The American College of Obstetricians and Gynecologists (ACOG) also concluded that neither thalidomide nor any drug should be prevented from being introduced or withdrawn from the market solely because it is teratogenic. Instead, ACOG strongly supports efforts to prevent exposure to known teratogenic agents in women who are pregnant or contemplating pregnancy.[20]

Thalidomide's resurrection provides an opportunity to determine whether some drugs are potentially so dangerous that their use *should* be restricted to the conditions for which the drug is FDA approved. So far this opportunity has been missed, but the birth of even one affected infant from off-label use will undoubtedly provoke this debate. As long as off-label uses are permitted, the FDA should insist not only that prescriptions for such uses be subject to the FDA's safeguards for approved uses but also that patients be informed that thalidomide has not been approved for the off-label use contemplated.

Approval of thalidomide is consistent with other FDA drug approvals. Many valuable drugs have potential teratogenicity, including warfarin, lithium, angiotensin-converting enzyme inhibitors, nonsteroidal antiinflammatory drugs, aminoglycosides, immunosuppressants, and antineoplastic drugs.[10,11] Even the Thalidomide Victims Association of Canada agreed to help Celgene obtain FDA approval for thalidomide, so long as steps are taken to fully inform physicians and patients and to try to prevent harm to fetuses. The organization successfully resisted thalidomide's being given a totally new name (Celgene wanted to call it Synovir; it will be marketed as Thalomid) and got the labeling changed from "Avoid pregnancy" to "Do not get pregnant."[21]

Learning From Tragedies

Not all tragedies can be redeemed, but we can learn from all tragedies. The FDA has the responsibility to ensure that thalidomide is safely introduced in the United States. But physicians and their patients must share responsibility for its proper use. Only if everyone meets these responsibilities is there a realistic opportunity to obtain the benefits of thalidomide and to minimize the risks by preventing birth defects. The FDA, for example, has recently been severely criticized for its performance in postmarketing monitoring of drug safety.[22,23] As more and more powerful drugs are approved for marketing, it has become apparent that much more careful postmarketing monitoring is needed than has been tolerated to date. In the absence of careful monitoring, many powerful drugs—such as the new diabetes drug troglitazone, which can cause severe liver toxicity—would have to be banned as unsafe.[24] Physicians have a central role in postmarketing monitoring and should prescribe thalidomide only after determining that it is the best drug for a serious condition and counseling fertile women patients to avoid pregnancy. And fertile women should take all reasonable steps to avoid pregnancy while taking thalidomide.

The *Titanic* can be reconstructed as myth but not raised intact (it is in 2 pieces). Thalidomide, because of changes in both law and medical technology, can be raised from its mythical monster drug status and reintroduced as a therapeutic component of modern medicine. Like preventing death at sea, preventing thalidomide-affected births will require not only medical technology but also human alertness. The decision to use thalidomide should be based on a realistic assessment of risks and benefits, as well as specific FDA, physician, and patient action to minimize predictable harm to fetuses.

The major lesson that the *Titanic* disaster holds regarding thalidomide is that wrapping a tragedy in the myth of a love story can obscure its horror and transform a tragic lesson into entertainment. FDA approval of thalidomide itself comes packaged as a mythical, although somewhat more complex, love story. Randy Warren, an affected child of a mother who took the drug, has dramatically argued in support of FDA approval: "Our hearts tell us this [thalidomide] did horrible things to our mothers and to ourselves, but our heads tell us 'How can we deny it to people who are suffering?'"[21] The myth, of course, is that society and the FDA have ever cared deeply about the suffering of people with Hansen's disease, when historically the United States has isolated "lepers" in "leper colonies" and left them to fend for themselves with the help of private charity.[25] Similarly, women with AIDS in the United States were denied zidovudine for years because of the fear that it was teratogenic.

Society is perfectly capable of being indifferent to human suffering and would continue to be in this instance if a private corporation, Celgene, had not thought it could profit from manufacturing and selling thalidomide. Ignoring commercial and profit motives here could lead to complacency in monitoring and result in the same type of disaster as the sinking of the *Titanic*. The *Titanic*'s owners reduced the number of lifeboats to save money, and the crew was unfamiliar with their operation.[1] The *Titanic*/thalidomide lesson for the FDA and public health is that continuous vigilance is required to ensure that all reasonable steps are taken to avoid predictable and preventable disasters. For the safety of the public's health, this broad lesson should be applied by the FDA, physicians, and drug companies to require rigorous postmarketing monitoring of all new and potentially dangerous drugs. □

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