

Dr. Frances Kelsey:
Turning the Thalidomide Tragedy
into Food and Drug Administration Reform

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“There was something a little different about this one so it seemed better to be safe and sure.”¹

—*Dr. Frances Oldham Kelsey on blocking Thalidomide’s U.S. drug approval*

“... [C]an we learn from this lesson; or can mankind educate itself only by disaster and tragedy?”²

—*Sen. Paul Douglas on Kefauver-Harris Amendments to the Food and Drug laws, Aug. 8, 1962*

After World War II, spectacular leaps in synthetic drug technology opened an era of “wonder drugs.” Laboratory-synthesized chemicals offered the hope, and sometimes the means, to cure every ill, from indigestion to deadly diseases. The pace of pharmaceutical growth was neither safe nor sure. Drugmakers surged ahead virtually unchecked because governments were reluctant to impede the next miracle-in-a-bottle and its economic rewards. Unscrupulous drugmakers exploited weak regulations by minimally testing new products, such as Chemie Grünenthal’s lucrative sedative thalidomide. Soon Grünenthal learned, then concealed, thalidomide’s tragic side-effect: deformed fetuses. By 1962, thousands of birth defects exposed this international disaster. Since thalidomide had never appeared in U.S. drugstores, Americans assumed their laws had blocked its sale. In fact, their regulatory agency, the Food and Drug Administration, was out-of-date, underfunded, and obsequious to drugmakers. Soon people learned that only a skeptical novice FDA investigator, Dr. Frances Kelsey, had spared them — not laws. Furthermore, thousands of Americans had ingested unlabeled thalidomide tablets under the guise of clinical testing — no law protected them from being guinea pigs. Shocked into action, and impressed by Dr. Kelsey’s demand for proven safety and accountability from thalidomide’s manufacturers, Congress strengthened drug regulation. From thalidomide’s tragedy, Dr. Kelsey inspired a public health triumph.

Thalidomide originated in West Germany after WWII. The War’s destruction heightened European demand for antibiotics and stress-relievers, so West Germans, needing physical and economic recovery, let pharmaceutical companies flourish unfettered.³ No worldwide drug safety testing standards existed, and with the advent of synthetic drugs, the medical community debated what the standards should be.⁴ Despite the lack of regulation and standards, many West German pharmaceutical firms had reputations for safe products; however, Chemie Grünenthal, founded in 1946, did not. Scientists criticized Grünenthal’s early products for “being used in man before thorough experiments on animals had been published,” causing numerous fatalities.⁵ A chronicle of blunders also produced thalidomide. Synthesized

accidentally in 1954 by Grünenthal, thalidomide seemed to have structural analogies to barbiturates, so it was tested on rats as a sedative, but none fell asleep; neither was it lethal at high dosages (*Figure 1*). Grünenthal mistakenly attributed this to nontoxicity — later found to be due to nonabsorption. Eventually, chemists found thalidomide-drugged rats were, at least, less active. Brief clinical testing showed thalidomide did induce sleep in humans. This elated Grünenthal executives because the drug performed like barbiturates with the unique advantage of nontoxicity.⁶ In 1958, thalidomide headed for over-the-counter sales in West Germany, marketed as “completely safe” for all (*Figure 2*). By 1961, forty-six countries sold the drug under fifty-one names (*Appendix*). Unfortunately, thalidomide’s full properties remained enigmatic; when a doctor asked its fetal effects, Grünenthal answered: *unknown*.⁷



Figure 1. Thalidomide is the generic name for α -phthlimidoglutarimide. Contergan is one of its many trade names.

Grünenthal showed a lack of accountability as thalidomide’s “completely safe” claims began to

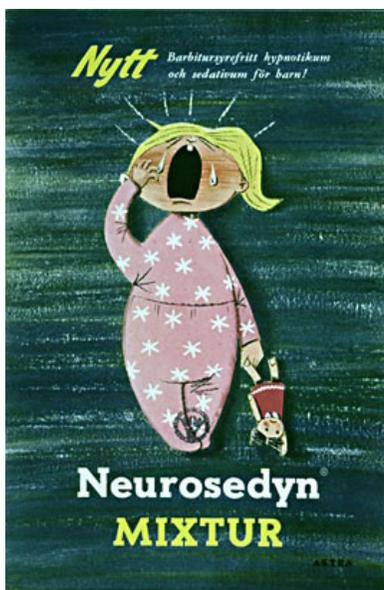


Figure 2. A 1961 Swedish advertisement for a liquid form of thalidomide touting it as a completely safe sedative, even for children.

crumble. In October 1959, complaints trickled in of peripheral neuropathy (limb nerve damage) in thalidomide’s long-term users. Grünenthal dismissed this as rare and reversible if dosage stopped. The reports, however, multiplied and cast doubt on reversibility. “If I were a doctor, I would not prescribe Contergan [thalidomide] any more,” confided the firm’s research director, Heinrich Mückter; “I see great dangers.”⁸ Epitomizing corporate greed, Grünenthal kept its secret but expanded thalidomide’s market as a hedge against future restrictions. Eyeing the lucrative U.S. market, they requested

FDA approval for sales in 1960. Meanwhile, Grünenthal deceitfully told doctors reporting neuropathy that theirs were among the first complaints. Soon, medical journals broadcast the news.⁹ In August 1961, West Germany restricted thalidomide to prescription sales. Grünenthal reluctantly removed *nontoxic* from the label.¹⁰

But another disaster loomed. Doctors often prescribed thalidomide to relieve pregnant women's nausea. A year after thalidomide's introduction, rare infant deformities increased, especially phocomelia: malformed or missing limbs (*Figure 3*). At first it seemed just chance, but doctors who never expected to witness phocomelia delivered several cases each month; by 1961, its incidence exceeded two-hundred times normal.¹¹ Dr. Widukind Lenz surveyed German doctors and mothers, finally pinpointing the cause: thalidomide, taken in early pregnancy, perhaps before pregnancy was suspected.¹² Lenz alerted the West German press. Grünenthal vilified him as a "half-wit" intent on "murdering a drug by spreading rumor."¹³ In November 1961, responding to public pressure but denying guilt, Grünenthal halted German thalidomide sales yet continued international marketing through January 1963, until the news reached each country, and bans were imposed.¹⁴ By then, over 13,000 babies suffered phocomelia.¹⁵

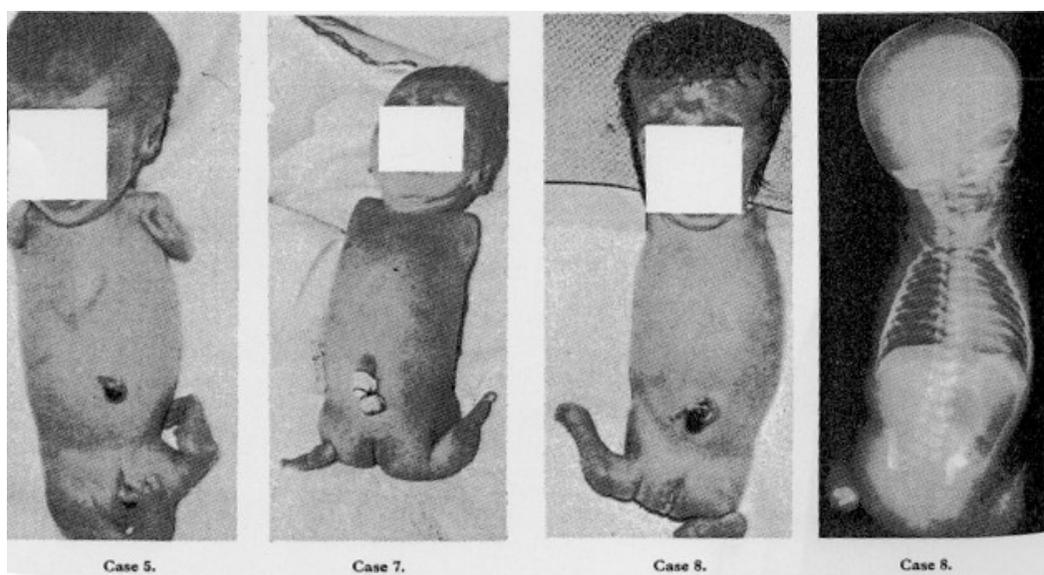


Figure 3. Babies with severe cases of phocomelia. This deformity is very rare naturally but is a common side-effect when thalidomide is taken during early pregnancy.

The U.S. could easily have been afflicted as well. In the 1950s, Americans were enthralled with pharmaceuticals, not just to cure diseases, but to soothe the stress of coping with the arms race, space race, and everyday rat race. Drugmakers enticed doctors to prescribe their latest products and reaped the rewards. By 1960, prescription drugs netted \$5 billion annually, quadrupling in a decade.¹⁶ America's drug regulatory agency, the FDA, was ill-equipped to control this booming industry because its mandate stemmed from minimal responses to tragedies. In 1906, unsanitary meat-packing conditions motivated

America's first domestic food and drug regulation, prohibiting adulterated and mislabeled products, but inspectors could only publish findings, not impose fines. In 1937, deaths from an untested formulation of Elixir Sulfanilamide led to laws requiring premarketing drug tests.¹⁷ In 1960, American drug regulation lacked muscle in three key areas: proof of safety and efficacy, test regulation, and accountability. The FDA had sixty days to prove a new drug unsafe, based on the company's tests; otherwise, approval was automatic. Efficacy was not considered. Drugmakers controlled testing, so clinical experiments could be performed without the FDA's or the subject's knowledge or consent. After approval, a drug's records, including side-effect reports, were company-private. Any FDA charges of misleading advertising or labeling had to be proved in court. Budget cuts in the 1950s left only 26 drug investigators, fewer than before WWII.¹⁸ Pharmaceutical companies had the upper hand, legally and financially.

The FDA was also steeped in controversy for favoring drugmakers. Commissioner George Larrick, a former food inspector, was appointed in 1954 "largely because the drug industry came to his support."¹⁹ Allegations of collusion surfaced: FDA doctors wrote promotional journal articles, and FDA officials ordered investigators "to certify a new drug on the grounds that the drug company itself was the best judge of its safety."²⁰ In 1960, thalidomide's application was submitted to this industry-biased FDA.

A debate on stronger drug regulations started in December 1959, but arguments primarily targeted pricing. Senator Estes Kefauver, a populist Democrat, sought to reduce drug prices, but he also addressed a key safety issue: drugs must be proven to be safe and effective by their producers, shifting the burden of proof from the FDA. Opponents decried his measures as "sufficiently drastic to kill not only this particular patient but the whole concept of free enterprise."²¹ In early 1962, Kefauver's bill languished in Congress.²² Meanwhile, some American doctors distributed thalidomide to unsuspecting patients in clinical tests. In February, *Time* briefly reported on Europe's thalidomide tragedy, noting "cautious Food and Drug Administration confined [thalidomide] to medical researchers for 'investigational use only.'"²³ Americans reacted with sympathy but also with relief that they were spared. The tragedy rekindled interest in Kefauver's bill, but President Kennedy proposed removing its pricing controls and trimming its safety measures to speed approval.²⁴ Kefauver balked at this, while others questioned if any bill was

necessary because, seemingly, current laws had averted thalidomide.²⁵ Congressional yammering continued as Americans' interest waned.

But what had kept thalidomide from American drugstores? On July 15, 1962, a *Washington Post* story, “Heroine of FDA Keeps Bad Drug Off of Market,” shocked Americans with the answer.²⁶ Only the right person, in the right place, at the right time had saved them from tragedy. The heralded heroine was Dr. Frances Oldham Kelsey (*Figure 4*). Tenacious and scientifically astute, she thwarted FDA shortcomings by insisting that thalidomide’s drugmaker prove its safety with scientifically-sound testing and account for any complaints *before* she would accept its application for marketing license. This effectively blocked it from American sales.

Kelsey, born in British Columbia in 1914, earned a Master’s degree in Pharmacology at McGill University and a PhD in Pharmacology at the University of Chicago. While in Chicago, she learned the importance of thorough testing. She aided the FDA’s study of Elixir Sulfanilamide, the drug that precipitated the Federal Food, Drug, and Cosmetic Act of 1938.

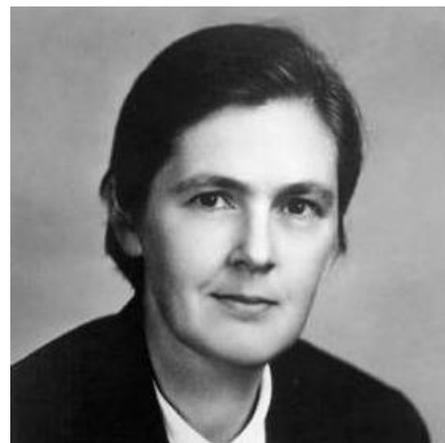


Figure 4. Dr. Frances Oldham Kelsey.

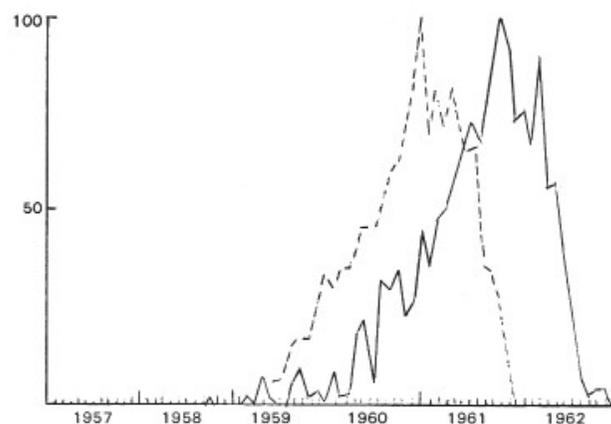
During WWII, Kelsey and others investigated anti-malarial drugs to aid Pacific jungle fighting. Kelsey saw that quinine crossed placental boundaries and that adults and fetuses metabolized the drug differently. In 1943, Frances married Dr. Fremont Ellis Kelsey, also a pharmacologist, then spent several years earning an MD. Kelsey also reviewed articles for *The Journal of the American Medical Association*, learning to distinguish scientific discourse from testimonials motivated by drugmaker money.²⁷ These experiences later helped her thwart thalidomide.

In August 1960, the FDA hired Kelsey as a new drug application investigator. With her expertise in pharmacology, she was well-qualified for her first assignment: an application for Kevadon, one of the trade names of thalidomide, submitted by William S. Merrell Corporation of Ohio, a Grünenthal distributor. “They gave it to me,” Kelsey recalled, “because they thought it would be an easy one to start on.”²⁸ She could have easily justified approval — after all, it was being sold in 46 countries — but she

was suspicious of this “peculiar drug” because of its differing effects on humans and animals and its lack of long-term testing.²⁹ “The clinical reports,” Kelsey felt, “were more on the nature of testimonials rather than the results of well-designed, well-executed studies.”³⁰ Since it was not a life-saving drug, just a sedative, she believed extra time could be taken for safety’s sake.³¹ With the sixty-day automatic approval imminent, Kelsey exploited an FDA loophole: she pronounced the application incomplete and “considered withdrawn,” with the approval period to begin upon completion. For the next 19 months, despite 58 interactions with Merrell, threats to her professional reputation and position, and complaints to her superiors, Kelsey would not be bullied into acceptance.³² She forced the burden of proof on Merrell.

In those 19 months, thalidomide’s “well-designed, well-executed studies” came from medical journals and colleagues, not Merrell. In February 1961, by chance, while perusing the previous December’s *British Medical Journal*, a letter implicating thalidomide in peripheral neuropathy caught Kelsey’s eye. Since Merrell had not mentioned this, she guessed they were concealing more. In May, based on her experiences with quinine, Kelsey asked Merrell about thalidomide’s fetal effects, but in late 1961, Dr. Lenz provided the tragic answer.³³ Merrell followed Grünenthal’s lead, dismissing the neuropathy as rare and reversible, and the teratogenicity as unsubstantiated. Again, Kelsey exceeded FDA laws and demanded accountability from Grünenthal through Merrell, insisting on full disclosure of side-effects. In March 1962, faced with mounting evidence, Merrell withdrew thalidomide’s application (*Figure 5*).³⁴

Americans, however, still faced tragedy — that is why Kelsey publicized her story. Since 1959, Merrell had been abusing another FDA weakness: unregulated clinical testing. Merrell used it as a ploy to familiarize physicians with thalidomide before FDA approval.³⁵ Distributing 2.5 million thalidomide tablets to 1,267 physicians, Merrell stated: “We



Graph showing the relation between the malformations of the thalidomide type and the sales of thalidomide (figures for Germany excluding Hamburg).

--- Thalidomide sales (January 1961 = 100)
 — 845 abnormalities of the thalidomide type (October 1961 = 100)

Figure 5. This graph depicts the 9-month lag between relative levels of thalidomide sales and deformed babies, providing evidence of thalidomide’s affect on fetuses.

have firmly established the safety, dosage and usefulness” and doctors “need not report results.”³⁶ Merrell learned of Grünenthal’s withdrawal of thalidomide in late 1961 but felt “no causal relationship between thalidomide and teratogenic effects had been established” so they made only cursory efforts to notify clinical investigators through July 1962.³⁷ Commissioner Larrick, unaware of the tests’ magnitude, trusted Merrell to warn physicians. In March 1962, Merrell sent letters to some doctors suggesting they restrict thalidomide from premenopausal women but did not recall the pills. The subjects, even if they realized the danger, might still have unknowingly used thalidomide because the bottles were unmarked or labeled with a trade name. In February, Kelsey pressed Merrell for the clinical investigators’ names, and in April she received a list that topped 1,000 — quadruple any previous U.S. clinical experiment. Convinced of thalidomide’s teratogenicity by American pediatrician Dr. Helen Taussig’s investigation of Lenz’s studies, Kelsey worried about Merrell’s half-hearted warnings. She could not — and the FDA’s top echelon would not — force a recall.³⁸ In July, someone familiar with her struggles alerted Kefauver, who was nearly resigned to the dilution of his drug regulation bill. Showing political savvy, his office tipped off the *Post*.³⁹ Three days after Kelsey’s story appeared, Larrick assigned 200 agents to thalidomide’s FDA recall. President Kennedy alerted the public. They were shocked that about 20,000 Americans had unknowingly ingested thalidomide in a marketing ploy.⁴⁰ Due to inadequate regulations that even Dr. Kelsey couldn’t thwart, about forty American babies were damaged by thalidomide.⁴¹

Critics of the FDA, then and now, contend Grünenthal made routine efforts to test thalidomide’s safety, and they label Kelsey as a “delay-causing bureaucrat” whose unreasonableness paid off.⁴² Refuted by records of the FDA, and Grünenthal and its distributors, thalidomide’s pre-marketing tests were uncommonly sparse for the era and sometimes deceitful. These records also confirm Kelsey acted appropriately based on her scientific knowledge.⁴³

Dr. Kelsey’s victory over thalidomide focused attention on drug regulation. She appeared in newspapers and magazines and on television.⁴⁴ People appreciated her candor. Her opinions were based on experience and logic, and apolitical. In Congressional hearings, Larrick was asked to explain the tardy

recall; Kelsey was asked for input on improving drug regulation.⁴⁵ After three years of debate on idealized safety measures, through her actions, Kelsey had provided a model for effective drug regulation.

Kefauver triumphantly resurrected the drug safety portion of his bill, adding measures to address the inadequacies Kelsey exposed. The bill abolished the automatic approval time limit, shifting the burden to the drugmakers to scientifically prove that a new drug is safe and effective using the best contemporary methods. Clinical tests required FDA approval and monitoring, and subjects had to give informed consent. Drugmakers had to share records pertinent to drug safety and efficacy, through development, test, and manufacture. The bill also allowed the agency to set manufacturing, advertising, and drug labeling rules, and to immediately recall hazardous drugs.⁴⁶ These monumental changes shifted the balance of power from the multi-billion dollar industry to the FDA. Lacking legislative support because of its shameful role in the tragedy, the industry conceded.⁴⁷ The Kefauver-Harris Amendments to the Food and Drug Act unanimously passed in the House and Senate. President Kennedy signed them with Dr. Kelsey present, on October 10, 1962, less than three months after the “Heroin” article’s publication.⁴⁸

This milestone was a triumph for public health, bringing not only stronger laws but also a change in the FDA’s direction. Dr. Kelsey demonstrated, and Congress legislated, that the FDA’s mission of protecting public health must be based on science. The FDA immediately began to evolve to support evaluation of new drugs and surveillance of existing drugs; it created an Investigational Drug branch to regulate clinical testing, appointing Dr. Kelsey director. Leadership changed; in 1966, Dr. John Gardner became its first Commissioner with a medical degree, signaling scientific qualifications mattered.⁴⁹ A crucial change, however, was that the FDA gained its own watchdog: the citizens. Kelsey advocated for citizens by publicizing thalidomide’s near miss; however, citizens returned the favor by advocating for reform of the FDA vulnerabilities she exposed. Between 1938 and 1962, public apathy eroded drug regulation, evidenced by Kefauver’s long battle for improvement. Through Kelsey’s actions, people realized vigilance is critical. Today, the FDA remains in the public eye, regulating \$1 trillion in products, and processing 200,000 reports of harmful drugs and medical devices annually. While the FDA will never

be above criticism, according to historian Philip Hiltz, “It is the most known, watched, and imitated of regulatory bodies.”⁵⁰ Tragedies like thalidomide happen when no one is watching.

Tragically altered bodies challenged thalidomide’s victims, their families, and their communities with medical procedures, prostheses, special schools, divorces, suicides, infant mercy killings, abortions, court battles, financial ruin, and anguish. Still, the true villain of this tragedy was never thalidomide; in fact, lately, it is considered one of the triumphs. Intently studied because of its teratogenicity, scientists discovered uses for thalidomide in leprosy, cancer, and AIDS. In 1998, with Kelsey on the investigation committee, the FDA finally approved thalidomide for limited use.⁵¹ There were, however, two villains. The first was corporate greed. Grünenthal clung to the drug’s market for profit, not benefaction.⁵² Ideally, business should have a conscience, but its duty is profit. The second culprit was inadequate drug regulation. Thalidomide preyed upon countries whose governments let economic gains take precedence over their duty: protecting the public. In this regard, America was guilty, but by luck, was reformed because of Dr. Frances Kelsey, who understood her mission.

Crediting Dr. Kelsey with sparing thousands of Americans from thalidomide’s tragedy, President Kennedy awarded her America’s highest civilian honor, the President’s Medal for Distinguished Federal Civilian Service.⁵³ But her legacy does not stop there. She affected people worldwide by providing a model and motivation for drug regulation agencies to rely on science, not politics, to protect public health. We need not educate ourselves only by disaster and tragedy — being safe and sure will lead to triumph.

Appendix: Countries where Thalidomide was Available

Sold in:

Angola
Argentina
Australia
Austria
Belgium
Brazil
Canada
Canary Islands
Cyprus
Denmark
Finland
Ghana
Great Britain
Guinea
Hong Kong
Iran
Iraq

Ireland
Israel
Italy
Japan
Jordan
Lebanon
Malaysia
Malta
Mexico
Mozambique
Netherlands
New Zealand
Norway
Pakistan
Peru
Portugal
Saudi Arabia

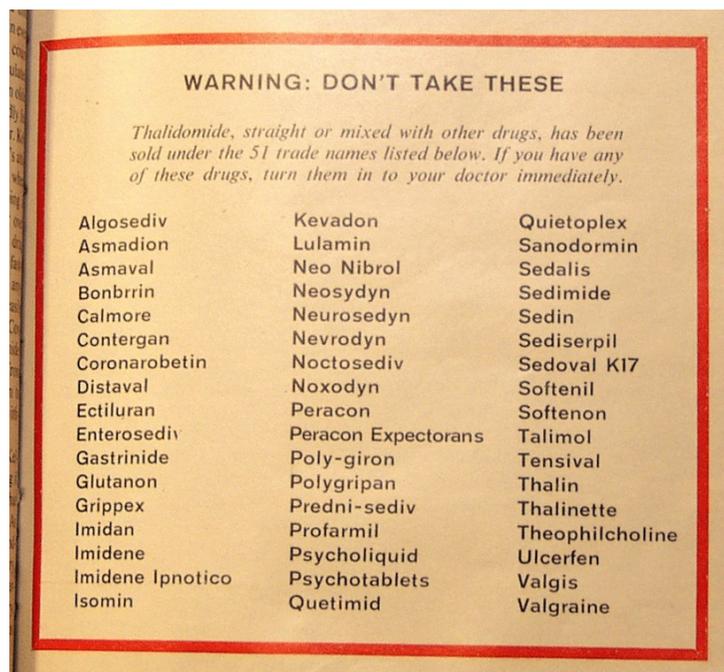
Singapore
Somalia
Spain
Sudan
Sweden
Switzerland
Syria
Taiwan
West Africa
West Germany

Not sold but available in:

Dominican Republic
France
Hungary
United States

Source: *The Many Faces of Thalidomide* by Randolph Warren.

Trade Names of Thalidomide



Source: LIFE magazine, August 10, 1962, page 29.

Notes:

Abbreviations used:

BPO: *By Prescription Only* by Morton Mintz

FDA: United States Food and Drug Administration

FK: Dr. Frances Oldham Kelsey

NYT: *The New York Times*

SPPP: *Saint Paul Pioneer Press*

T&P: *Thalidomide and the Power of Drug Companies* by Henning Sjöström & Robert Nilsson

¹ Linda Bren, “Frances Oldham Kelsey: FDA Medical Reviewer Leaves her Mark on History,” *FDA Consumer*, March–April 2001, from FDA website, available from http://www.fda.gov/fdac/features/2001/201_kelsey.html, accessed 1 February 2007.

² U.S. Congress, Senate, Senator Douglas after vote on Amendments to the Federal Food, Drug, and Cosmetic Act, S. Res. 1552, 87th Cong. 2nd sess. *Congressional Record* 108, pt. 12 (23 August 1962): 17422.

³ Europe’s post-WWII physical state, see: Trent Stephens and Rock Brynner, *Dark Remedy: The Impact of Thalidomide and Its Revival as a Vital Medicine* (Cambridge, MA: Perseus Publishing, 2001), 2–5; West Germany’s post-WWII economics, see: Henning Sjöström and Robert Nilsson, *Thalidomide and the Power of the Drug Companies* (Middlesex, England: Penguin Books, 1972), 30–1.

⁴ Frances O. Kelsey, interviewee, “Inside Story of a Medical Tragedy,” *U.S. News & World Report*, 13 August 1962, 55; Committee on Public Health, New York Academy of Medicine, “Where Is Science Taking Us?” *Saturday Review*, 1 September 1962, 44–5; “New Drugs — How Good are the Safeguards.” *U.S. News & World Report*, 13 August 1962, 56–7; Stephens, 108–9; G. F. Somers, “Thalidomide and Congenital Abnormalities (Letter to the Editor),” *Lancet* 1 (28 April 1962): 912–3.

⁵ Insight Team of *The Sunday Times* of London, *Suffer the Children: The Story of Thalidomide* (NY: Viking Press, 1979), 10–11; “being used in man...” quoted in *T&P*, 35.

⁶ Rodent tests, see: Insight Team, 15–21; G. F. Somers, “Pharmacological Properties of Thalidomide (α -Phthalimidido Glutarimide), a New Sedative Hypnotic Drug” *British Journal of Pharmacology* 15 (1960): 111; Clinical tests, see: D.M Burley, T.C. Dennison, and Walford Harrison, “Clinical Experience with a New Sedative Drug,” *Practitioner* 183 (1959): 57–60; Louis Lasagna, “Thalidomide — A New Nonbarbiturate Sleep-inducing Drug,” *Journal of Chronic Disorders* 11 (June 1960): 627–31; Morton Mintz, *By Prescription Only*, 2nd ed. (Boston: Houghton Mifflin Co., 1967), 149–51.

⁷ Marketing, see: Insight Team, 29–32; *T&P*, 33, 37, 43–5; Helen B. Taussig, “The Thalidomide Syndrome,” *Scientific American* 207 (August 1962): 35; Randolph Warren, “The Many Faces of Thalidomide,” 7 May 1999, from Thalidomide Victims Association of Canada website, available from <http://www.thalidomide.ca/en/information/faces.html>, accessed 19 February 2007, 1–6; Enigma, see: *T&P* 95–6.

⁸ Heinrich Mückter, Chemie Grünenthal staff meeting notes, 14 July 1961, quoted in *T&P*, 88.

⁹ Peripheral neuropathy background and company documents, see *T&P*, 46–93; Journal articles, see: A. Leslie Florence, “Is Thalidomide to Blame?” *British Medical Journal* 2 (31 December 1960): 1954; Pamela M. Fullerton and Michael Kremer, “Neuropath after Intake of Thalidomide (Distaval),” *British Medical Journal* 2 (30 September 1961): 855–8.

¹⁰ *T&P*, 91–3.

¹¹ Taussig, 29; W. G. McBride, “Thalidomide and Congenital Abnormalities (Letter to the Editor).” *Lancet* 1 (16 December 1961): 1358; idem, “The Teratogenic Action of Drugs.” *Medical Journal of Australia* (26 October 1963): 690–1; Insight Team, 99; Philip J. Hilts, *Protecting America’s Health: The FDA, Business, and One Hundred Years of Regulation* (NY: Alfred A. Knopf, 2003), 154–5.

¹² W. Lenz, "Thalidomide and Congenital Abnormalities (Letter to the Editor)," *Lancet* 1 (6 January 1962): 45–6; Anthony White, "German Doctor Linked Drug to Deformities," *SPPP*, 12 August 1962, 1st section, 10; A.L. Speirs, "Thalidomide and Congenital Abnormalities," *Lancet* 1 (10 February 1962): 303–5; "Thalidomide and Congenital Malformations (Editorial)," *Lancet* 1 (10 February 1962): 307–8; G. F. Somers, "Thalidomide and Congenital Abnormalities (Letter to the Editor)," *Lancet* 1 (28 April 1962): 912–3.

¹³ "half-wit" quoted in Hiltz, 155; "murdering..." quoted in *T&P*, 101.

¹⁴ General info. on thal. and phocomelia, see: *T&P*, 94–111, 136–8; Grünenthal denial, see: R.O. Nulsen, "Trial of thalidomide in insomnia associated with the third trimester," *American Journal of Obstetrics and Gynecology* 81 (June 1961): 1245–8; Sales until 1963, see: *T&P* 146–8; Warren, "Many Faces," 1–3.

¹⁵ Hiltz, 158.

¹⁶ Stephens, 2–4; "Payola for Physicians," *Saturday Review*, 4 February 1961, 41–2; Seymour Freedgood, "The Reluctant Dragon of the Drug Industry," *Fortune*, November 1962, 224; "Drug Companies Reassured by U.S.," *NYT*, 16 February 1963, 7.

¹⁷ Hiltz, 72–94; William Patrick, *The Food and Drug Administration* (NY: Chelsea House Publishers, 1988), 26–32.

¹⁸ Clinical testing, see: "Thalidomide Pill was Tested in U.S.," *NYT*, 28 July 1962, 15; "Guinea Pigs and People (Editorial)," *Christian Century*, 15 August 1962, 975–6; *BPO*, 30–1, 148–50; Committee on Public Health, 44–5; FDA key weaknesses, see: John Lear, "A Report on the New Drug Bill in the U.S. Senate," *Saturday Review*, 4 August 1962, 35–6; "Tragedy From a Pill Bottle Some Sad Lessons Learned," *Newsweek*, 13 August 1962, 52–3; Hiltz, 118–9.

¹⁹ "largely because..." Rankin quoted in Hiltz, 120.

²⁰ "to certify..." quoted in "Dr. Kelsey's Predecessor Told Senators of Drug Perils in 1960," *NYT*, 10 August 1962, 6; FDA controversy, see: Lear, 35; Will Jonathan, "The Feminine Conscience of FDA: Dr. Frances Oldham Kelsey," *Saturday Review*, 1 September 1962, 42; "The Unfinished Story of Thalidomide," *Saturday Review*, 1 September 1962, 35; "Letter From a Retired Drug Inspector," *Saturday Review*, 4 February 1961, 43.

²¹ "sufficiently drastic..." Sen. Wiley quoted in "This Month's Feature: The Investigation of the Drug Industry," *Congressional Digest*, February 1962, 61.

²² Lear, 35–6; "This Month's," 35–64; "The Kefauver Hearings: The Drug Industry Finally has its Day and Does Quite Well," *Science*, 15 December 1961, 1968–70; Charles L. Fontenay, *Estes Kefauver: A Biography* (Knoxville: Univ. of Tennessee Press, 1980), 379–84.

²³ "Sleeping Pill Nightmare," *Time*, 23 February 1962, 86–7; *BPO*, 62–3.

²⁴ Rekindled interest in drug regulation, see: Robert B. Plumb, "Deformed Babies Traced to a Drug," *NYT*, 12 April 1962, 37; Kennedy strips Kefauver bill, see: "FDA seeks more muscle," *Business Week*, 10 March 1962, 122; U.S. Congress, Senate, President's Letter to Sen. Eastland on Amendments to Drug Laws, 87th Cong., 2nd sess., *Congressional Record* 108, pt. 12 (23 August 1962): 17371–2.

²⁵ J. B. Gorman, *Kefauver: A Political Biography* (NY: Oxford Univ. Press, 1971), 352–7; Fontenay, 385–9.

²⁶ Morton Mintz, "Heroine of the FDA Keeps Bad Drug Off of Market," *Washington Post*, 15 July 1962, 1.

²⁷ Kelsey biography, see: Bren, 1–7; Anti-malaria research, see: Taussig, 34; AMA reviewer, see: *DK*, 45.

²⁸ "They gave..." Kelsey quoted in Bren, 6.

²⁹ Mintz, "Heroine," 1.

³⁰ "The clinical reports..." Kelsey quoted in Bren, 2.

³¹ Mintz, "Heroine," 8.

³² Merrell bullies FK, see: John Mulliken, "A Woman Doctor Who Would Not Be Hurried." *Life*, 10 August 1962, 28–9. Official FDA record of Merrell – FK interactions, see: U.S. Congress, Senate, Thalidomide and other Drugs, 87th Cong., 2nd sess., *Congressional Record* 108, pt. 12 (8 August 1962): 15932–5.

³³ Mintz, "Heroin," 8; Neuropathy, see: Florence, 1954; Phocomelia, see: Lenz, 45–6; White, 10.

³⁴ Kelsey, 54–5; *BPO*, 248–55.

³⁵ "Unfinished Story," 38–40.

³⁶ "We have..." Merrell representative quoted in *BPO*, 150.

³⁷ *BPO*, 254; Carl A. Bunde, "A U.S. Drug Firm's Shock," *Life*, 10 August 1962, 29.

³⁸ *BPO*, 251–8; Hilts 150–1; Taussig, 29–35.

³⁹ Morton Mintz, Sr. Advisor to the Nieman Watchdog Project, E-mail interviews by author, 26 February 2007 and 5 April 2007; idem, "Morton Mintz on the collapse of Congressional oversight," 2 May 2005, available at Nieman Watchdog web-site, <http://www.niemanwatchdog.org.html>, accessed on 7 February 2007.

⁴⁰ "U.S. Considering Regulations to Reduce Peril of New Drugs," *NYT*, 29 July 1962, 44; "Kennedy says this about Thalidomide," *U.S. News & World Report*, 13 August 1962, 57; "Trial Drug Curb Sought By FDA," *SPPP*, 29 July 1962, 1st section, 1.

⁴¹ Hilts, 155–8.

⁴² "delay-causing bureaucrat" quoted from Stephen B. Harris, "The Right Lesson to Learn From Thalidomide," 1992, available from web-site <http://w3.uiuc.edu:8001/Liberty/Tales/Thalidomide.html>, accessed on 2 February 2007; Henry Hazlitt, "Overregulation," *Newsweek* 10 Sep. 1962: 86.

⁴³ Deceitful testing, see: R. O. Nulsen, "Trial of thalidomide in insomnia associated with the third trimester," *American Journal of Obstetrics and Gynecology* 81 (June 1961): 1245–8; Hilts 150–1; Kelsey acted appropriately, see: Fran Hawthorne, *Inside the FDA: The Business and Politics Behind the Drugs We Take and the Food We Eat* (Hoboken: John Wiley & Sons, Inc., 2005), 44; Hilts 152–3.

⁴⁴ "Television," *NYT*, 2 August 1962, 53; "Drug Market Guardian," *NYT*, 2 Aug. 1962, 12; Mulliken, 28–9.

⁴⁵ Larrick and Kelsey treated differently, see: United States, Congress, Senate, Committee on Government Operations, Subcommittee on Reorganization and International Organizations, Interagency Coordination in Drug Research and Regulation, Part 1[microform]: hearings before the U.S. Senate Committee on Government Operations, Subcommittee on Reorganization and International Organizations, 87th Cong., 2nd sess., pt. 1 (1 August 1962), 10–72; Kelsey is model for FDA reform, see: idem, Congress, Senate, Drug Legislation, 87th Cong., 2nd sess., *Congressional Record* 108, pt. 12 (9 August 1962): 16072–4; "Dr. Kelsey Calls for Tighter Restrictions on Drugs as Senate Hearings Open," *NYT*, 7 August 1962, 15; "Unfinished Story," 39–40.

⁴⁶ Marjorie Hunter, "Drug Curbs, Scoffed At in '60, Are Now Being Sped in Congress," *NYT*, 12 August 1962, 57; "Drug Fight enters final round," *Business Week*, 1 September 1962, 28–30; "Tighter rein on drug testing," *Business Week*, 12 January 1963, 76–80.

⁴⁷ "Tough drug law coming," *Business Week*, 11 August 1962, 37; Hazlitt, 86; "Announcements." *Science*, 17 August 1962, 5.

⁴⁸ U.S. Congress, Senate, Approval of Senate Bills and Joint Resolutions After Sine Die Adjournment, S. Res. 1552, 87th Cong., 2nd sess., *Congressional Record* 108, pt. 14 (13 October 1962): 23473; "New Drug Law," *Time*, 19 October 1962, 40.

⁴⁹ Marjorie Hunter, "Food and Drug Agency Faces Two Investigations in Congress," *NYT*, 14 October 1962, 82; idem, "Shake-up Asked for Drug Agency," *NYT*, 26 October 1962, 8, "Thalidomide Opponent Named to Head New U.S. Drugs Unit," *NYT*, 29 December 1962, 1; Hilts, 166.

⁵⁰ "It is the most..." and statistics quoted from Hilts, *xiv*.

⁵¹ Stephens, 111–61; Randolph Warren, "The Last Word — Living in a World With Thalidomide: A Dose of Reality," *FDA Consumer*, March–April 2001, from FDA website, available from http://www.fda.gov/fdac/departs/2001/201_word.html, accessed 19 February 2007.

⁵² *T&P*, 54–5.

⁵³ "Dr. Kelsey Receives Gold Medal From Kennedy at White House," *NYT*, 8 August 1962, 19.

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Special Note:

- Thalidomider is the designation preferred by those with thalidomide-induced birth defects.

Abbreviations used:

BPO: *By Prescription Only* by Morton Mintz

FDA: United States Food and Drug Administration

FK: Dr. Frances Oldham Kelsey

NYT: *The New York Times*

T&P: *Thalidomide and the Power of Drug Companies* by Henning Sjöström & Robert Nilsson

Primary Sources:

“Announcements.” *Science*, 17 August 1962, 5.

This announces a new Commission on Drug Safety established by the Pharmaceutical Manufacturers Association (PMA) comprised of industry leaders, physicians, journal editors, and academic scientists. This is interesting because it is the drug industry’s attempt to regain public confidence after bullying FK, and delaying the thalidomide recall.

Bunde, Carl A. “A U.S. Drug Firm’s Shock.” *Life*, 10 August 1962, 29.

This is a statement by the senior officers of the Wm. S. Merrell Co. after FK revealed Merrell’s attempt to market thalidomide. An interesting contrast to FK’s story, which appears on the facing page, it shows how Merrell tried to recover its image and minimize its role in the near-tragedy, and tried to cast doubt on the role of thalidomide in the birth defects.

Burley, D.M., T.C. Dennison, and Walford Harrison. “Clinical Experience with a New Sedative Drug.” *Practitioner* 183 (1959): 57–61.

This is a small short-term British clinical test on 83 unsuspecting patients, which like Lasagna (below) concludes that thalidomide “goes a long way towards being the ideal hypnotic” because it is tasteless, easy to take, no hangover, and is non-toxic in large doses (unlike other drugs that easily cause accidental or intentional overdose fatalities). Grünenthal used this to promote thalidomide’s safety; however like its other clinical tests, there is no investigation of the drug’s absorption, only outward behavior. This illustrates the incompleteness of thalidomide’s testing.

Committee on Public Health, New York Academy of Medicine. “Where Is Science Taking Us?” *Saturday Review*, 1 September 1962, 44–5.

This article is an excerpt of one published in June 1962, before the public was told of the thalidomide clinical tests. It discusses the lack of American or international medical testing standards, and how drug firms currently have the upper hand in clinical testing. It suggests ways that the FDA should correct it, including using investigators with MD and pharmacology degrees (like FK). This illustrates the state of testing in this era.

- “Dr. Kelsey Calls for Tighter Restrictions on Drugs as Senate Hearings Open.” *NYT*, 7 August 1962, 15.
This article outlines the safety measures that FK wants, such as no 60-day automatic approval. This is important because it shows that FK not only stopped thalidomide, she became a model for stronger drug reform, which is a point of this paper.
- “Dr. Kelsey Receives Gold Medal From Kennedy at White House.” *NYT*, 8 August 1962, 19.
FK was awarded the nation’s highest honor for a civilian Federal service, and this article describes the award ceremony. This is important because it illustrates the significance of her contribution to our nation.
- “Dr. Kelsey’s Predecessor Told Senators of Drug Perils in 1960.” *NYT*, 10 August 1962, 1+.
This article discusses Dr. Barbara Moulton’s 1960 testimony about the weak FDA laws and how the FDA had become a “service agency” for drugmakers. A quote is used to illustrate the power that drug companies had before the thalidomide tragedy.
- “Drug Companies Reassured by U.S.” *NYT*, 16 February 1963, 7.
This article appeared after the Kefauver-Harris Amendments passed. Kelsey and Larrick address 625 drug company representatives at a meeting to give details about the law. The information on the law’s implementation is generally useful, and specifically, the amount of pharmaceutical sales is used in this project.
- “Drug Fight enters final round.” *Business Week*, 1 September 1962, 28–30.
This is a useful comparison of the old regulations and the new Kefauver-Harris Amendments that are headed for law. The industry, while complaining about the new burden, seems resigned to the law, but recognizes that it puts the FDA firmly in control, which is one of the points in this paper.
- “Drug Market Guardian.” *NYT*, 2 August 1962, 12.
This article provides personal details on FK: her office, her home life, and background. It is important because it gives a glimpse of her character: shy, outwardly plain, but well-schooled, intelligent, and devoted to family. Also interesting to this project, FK says she has received many letters of thanks from people, with enclosed pictures of their healthy children, which demonstrates how popular she was; this helped her broadcast her ideas for FDA reform.
- “FDA seeks more muscle.” *Business Week*, 10 March 1962, 122.
This article is from the drug industry’s viewpoint. Written just after the first news of the thalidomide tragedy, it expects President Kennedy’s forthcoming drug bill to be less restrictive than Sen. Kefauver’s. It urges quick approval of Kennedy’s bill to avoid Kefauver’s. This is important to this paper because it shows the corporate point-of-view: minimize regulation.
- Florence, A. Leslie. “Is Thalidomide to Blame?” *British Medical Journal* 2 (31 December 1960): 1954.
The author describes why he suspects that long-term usage of the drug has led to numbness, cramping, and coldness of the extremities in his patients. He hints that withdrawal of the drug improved, but did not completely remove the symptoms. This is the letter that FK saw by chance which confirmed her suspicions about thalidomide.
- Freedgood, Seymour. “The Reluctant Dragon of the Drug Industry.” *Fortune*, November 1962, 140–2+.
This article highlights a generic drug manufacturer’s struggle to compete with the powerful trade-named drug producers. Generally useful is the information on the post-WWII “wonder drug” era, the naming of drugs, and how the Kefauver-Harris Amendment is affecting the drug industry. Statistics on the drug market are also used.

Fullerton, Pamela M. and Michael Kremer. "Neuropath after Intake of Thalidomide (Distaval)." *British Medical Journal* 2 (30 September 1961): 855–8.

This article appears as many reports of peripheral neuropathy and other effects on the nervous system are being tied to thalidomide. In contrast to earlier studies (see *Burley* and *Lasagna*), this is a thorough clinical test that attempts to find out how the body metabolizes the drug. It cites further studies that have recently appeared. This shows that, despite Grünenthal's efforts, news of thalidomide side-effects is being publicized.

"Guinea Pigs and People (Editorial)." *Christian Century*, 15 August 1962, 975–6.

This article is one of many that express shock that drugmakers' may clinically test drugs without FDA regulation and without patients' understanding and consent. This supports this paper's contention that there were major weaknesses in the FDA laws before the thalidomide tragedy.

Harris, Stephen B. "The Right Lesson to Learn From Thalidomide." 1992. Available from web-site <http://w3.uiuc.edu:8001/Liberty/Tales/Thalidomide.html>. Accessed on 2 February 2007.

This article argues that FK was just a delay-causing bureaucrat; also, that typical pre-marketing tests of the era had been performed on thalidomide and showed no birth deformities. These are common criticisms, but as this project shows, the historical record does not support them.

Hazlitt, Henry. "Overregulation." *Newsweek*, 10 September 1962, 86.

This article takes the drugmakers' side in the final battle against Kefauver's bill. It makes the usual arguments that regulation will impede important drug development and be extremely costly, and that drug investigators are bureaucrats with a political agenda. It has obvious errors, such as thalidomide did not affect pregnant animals, and more subtle ones, such as strong drug laws prevented thalidomide's U.S. tragedy (as this paper shows, FK did instead). This is important because it illustrates how drugmakers viewed the new laws.

Hunter, Marjorie. "Drug Curbs, Scoffed At in '60, Are Now Being Sped in Congress." *NYT*, 12 August 1962, 57.

This article contains an excellent chronology of Sen. Kefauver's struggles for improved drug safety regulations. This is important because it shows when power shifted from the drug industry, which would only back a weak safety bill, to the reformers who eventually managed to surpass the 1960 objectives. That turning point is FK's news story, and this supports this project's thesis.

_____. "Food and Drug Agency Faces Two Investigations in Congress." *NYT*, 14 October 1962, 82.

This article describes why Congress is investigating the FDA. Written after the new stronger regulations have been passed, FK and her predecessor, B. Moulton, are credited with inspiring this vigorous investigation of FDA weaknesses. This is important to the project because it shows another way that FK influenced change.

_____. "Shake-up Asked for Drug Agency." *NYT*, 26 October 1962, 8.

This article, like "Food and Drug" above, involves FDA investigation, but more specifically targets Larrick and his lack of scientific qualifications, and again mentions FK as an inspiration for the shake-up. This shows that FK influenced the FDA to be founded in science, not politics.

"The Kefauver Hearings: The Drug Industry Finally has its Day and Does Quite Well." *Science*, 15 December 1961, 1968–70.

This is a summary of the debate over tightened drug regulations, and includes viewpoints of the Amer. Med. Assoc.(AMA), the drug industry, the Administration, and Kefauver. The drug industry and AMA generally object or want more investigation on every issue. This is used to show the lack of momentum in the drug regulation debate before the thalidomide tragedy.

Kelsey, Frances O., interview. "Inside Story of a Medical Tragedy." *U.S. News & World Report*, 13 August 1962, 54–5.

Kelsey discusses the increased complexity of synthetic drugs and the difficulties in testing them. This is used to show the tenuous state of testing for drug safety in this era.

"Kennedy says this about Thalidomide." *U.S. News & World Report*, 13 August 1962, 57.

This is a transcript of a portion of a news conference on August 1. He makes two relevant announcements: first, he issues a warning to people to check for thalidomide in their medicine cabinets; second, he asks for stronger FDA laws (but still not as strong as the ones eventually passed). This is important because both of these developments came only days after FK reveals her story, which, this project contends, is why she revealed it: for stronger laws and a recall.

Jonathan, Will. "The Feminine Conscience of FDA: Dr. Frances Oldham Kelsey." *Saturday Review*, 1 September 1962, 41–3.

This article analyzes FK's invitees to the presentation of her Distinguished Federal Civilian Service Medal, and in doing so, discusses controversies in the FDA. This is used to support this paper's point that the FDA was industry-biased before the thalidomide tragedy.

Lasagna, Louis. "Thalidomide — A New Nonbarbiturate Sleep-inducing Drug." *Journal of Chronic Disorders* 11 (June 1960): 627–31.

This describes a short-term clinical test of thalidomide at Johns Hopkins Medical Center in 1959 and is an example of a test that Grünenthal used to promote thalidomide's safety and effectiveness. The 91 patients were unaware that they were part of the experiment. It concludes that thalidomide is effective, but there are side-effects of headache and nausea, however the result "arouses hope that thalidomide may represent a significant advance in hypnotic therapy." This illustrates how lightly thalidomide was tested on unwary subjects.

Lear, John. "A Report on the New Drug Bill in the U.S. Senate." *Saturday Review*, 4 August 1962, 35–6.

This report describes the weaknesses of the current FDA laws, and how the Kefauver bill will address them. It also refers to the investigation of the chief of FDA's antibiotic division accepting pay for work on antibiotics promotional journals. The weaknesses of the law and corrupt FDA behavior are both important points in this paper.

Lenz, W. "Thalidomide and Congenital Abnormalities (Letter to the Editor)." *Lancet* 1 (6 Jan. 1962): 45.

Dr. Lenz, who performed extensive investigations that led to the withdrawal of thalidomide in W. Germany, warns others about the risk of taking thalidomide between the 4th and 8th week of pregnancy. Distillers (thalidomide's British distributor) response is printed beneath; they believe that there is too little information to decide. Lenz's information, and the drugmakers reluctance to accept his conclusion are both useful to this project.

"Letter From a Retired Drug Inspector." *Saturday Review*, 4 February 1961, 43.

This letter, written before the tragedy, provides inside perspective on the FDA: easy on big drugmakers, hard on small ones, fear of consumer lawsuits, producer favored over consumer, lack of training of inspectors, discouragement of initiative. For this paper, it illustrates the weak character of the FDA prior to the thalidomide tragedy and the resulting FDA reforms.

McBride, W.G. "The Teratogenic Action of Drugs." *Medical Journal of Australia* (26 October 1963): 689–93.

This article details Dr. McBride's findings hinted at in his previous letter (below). Also interesting to this project, McBride states that all nontoxic drugs before thalidomide's tragedy were assumed to be safe during pregnancy; now that must be rethought and fetal testing should be done for all drugs. FK, with her quinine experience, did not make this assumption with thalidomide.

_____. "Thalidomide and Congenital Abnormalities (Letter to the Editor)." *Lancet* 1 (16 December 1961): 1358.

This letter, from a South Wales doctor, notes the high incidence of the rare deformities in babies whose mothers took thalidomide and asks others if they have seen this. Published a month after West Germany discontinued sales of the drug, this is the first letter in medical journals about the deformities, illustrating this era's communication gap in the medical community. Also interesting: a postscript by the *Lancet* editor says Distillers (thalidomide's British distributor) recognizes the possible implication of the drug, and thalidomide has been withdrawn from the British market.

Melendez, Tony. *A Gift of Hope*. San Francisco: Harper & Row, 1979.

A native of Nicaragua, the author is a Thalidomider, but he is also an accomplished vocalist and guitarist. He describes living with his deformities. This is important because it demonstrates why it is vital to remember FK's contributions — to prevent future tragedies.

Mintz, Morton. *By Prescription Only*. 2nd ed. Boston: Houghton Mifflin Co., 1967.

This is an analysis of the FDA in the 1950s to mid-1960s. It provides more details and analysis of the events than in his "Heroine..." article below, especially about FDA controversies, and the delayed recall of U.S. thalidomide dispensed under the guise of clinical testing. It also supports this project's assertion that FK was strong where the FDA was weak.

_____. Sr. Advisor to the Nieman Watchdog Project. E-mail interviews by author. 26 February 2007 and 5 April 2007.

Mr. Morton is the *Washington Post* staff reporter that first interviewed FK about her thalidomide involvement and the author of articles and books on the FDA in the era of this project. Mr. Morton and his works are very important resources not only on FK's actions, but also on the U.S. political events in this era of FDA reform. He provided insight on why FK came to the media with her story, and details pertinent to that event. FK's motivation to tell her story is a key element of this project.

_____. "Heroine of the FDA Keeps Bad Drug Off of Market." *Washington Post*, 15 July 1962, A1+.

This is the newspaper article that introduced FK to the public, and shocked America with how close they had come to thalidomide's tragedy. It is useful because it relates her actions in blocking thalidomide from FDA approval.

_____. "Morton Mintz on the collapse of Congressional oversight." 2 May 2005. Available at Nieman Watchdog web-site. <http://www.niemanwatchdog.org.html>. Accessed on 7 February 2007.

This article provides first-hand details on how the FK story "Heroine..." came to the *Washington Post*. This is critically important because it links Sen. Kefauver's political efforts to strengthen the FDA with FK's actions.

Mulliken, John. "A Woman Doctor Who Would Not Be Hurried." *Life*, 10 August 1962, 28–9.

An interview with FK's details her battle with Merrell's agents as they bullied her for FDA approval of thalidomide, giving a glimpse of her personality: straightforward, with a sense of duty and humor. This information is used in this paper.

"New Drug Law." *Time*, 19 October 1962, 40.

This describes the newly-signed Kefauver-Harris Amendments to the Food and Drug Laws and discusses the possible implications on the public and industry. Attesting to FK's impact on this law, a photograph of FK being handed the signing pen by the President illustrates the article.

“New Drugs — How Good are the Safeguards.” *U.S. News & World Report*, 13 August 1962, 56–7. These are excerpts from a Senate subcommittee hearing address the FDA’s role in the thalidomide case. The excerpts from Larrick and FK deal with the general lack of expertise in clinical testing. This is used to show the state of drug safety testing in this era.

Nulsen, R.O. “Trial of thalidomide in insomnia associated with the third trimester.” *American Journal of Obstetrics and Gynecology* 81 (June 1961): 1245–8.

This article was submitted to FK to prove thalidomide’s safety. It analyzes other clinical trials (like *Lasagna* and *Burley*) of late-term pregnancy (phocomelia occurs early-term) intended to prove safety. A close reading shows that not all subjects are pregnant, and most studies (including one by the drug’s creators) merely analyze outward behavior. Worse than bad science, during subsequent court cases, it was found that Merrell’s medical director and his secretary wrote this, not Nulsen. It illustrates the depth of the drugmaker’s deceit to maintain profitability.

“Payola for Physicians.” *Saturday Review*, 4 February 1961, 41–2.

This is a copy of an advertisement for a free sun lamp kit if doctors order the drug Theelin; no description of what the drug actually does is given. The recipient notes that this is a new sales tactic. He is insulted by the implication that a doctor would prescribe a drug to get the free prizes. This is an example of the intense drug marketing in this era.

Plumb, Robert B. “Deformed Babies Traced to a Drug.” *NYT*, 12 April 1962, 37+.

In this article Dr. Taussig, who has investigated the European thalidomide tragedy, gives details of the tragedy and attempts to rekindle interest in Kefauver’s bill for stronger U.S. drug regulation. It is one of the first U.S. *newspaper* articles on the tragedy (See “Sleeping” below).

Pringle, M. L. Kelmer, and D.O. Fiddes. *The Challenge of Thalidomide (Studies in Child Development)*. London: Longman Group, 1970.

This details a study of elementary school-aged Thalidomiders in mental, emotional, and physical development. Intellectually, they are no different than their peers, but the challenges are great otherwise. This is important because it demonstrates why it is vital to remember FK’s contributions — to prevent future tragedies.

Roskies, Ethel. *Abnormality and Normality: The Mothering of Thalidomide Children*. Ithaca: Cornell University Press, 1972.

This is a study of Canadian Thalidomiders and their mothers. Canada provides special care for the Thalidomiders. This book details some of the mistakes that caregivers made (i.e. holding things with feet was taboo; they were forced to use less effective prostheses instead). This provides perspective on the people who suffered the most in this tragedy.

Sjöström, Henning and Robert Nilsson. *Thalidomide and the Power of the Drug Companies*. Middlesex, England: Penguin Books, 1972.

This is one of the most important resources about the start of the thalidomide tragedy. Nilsson is a research chemist. Sjöström is a Swedish lawyer who actively worked on the prosecution of Chemie Grünenthal, and had first-hand access to their private files that were seized from the company. This book contains English translations of those files. Generally useful to this project is the information about the creation, and the rise and fall of thalidomide in Germany. A translated quote from Heinrich Muckter appears in the project: “I see great dangers...” from a staff meeting. Also, the quote “Being used in man...,” from a West German journal of medicine, illustrates the company’s poor reputation for drug safety testing. *Aside*: This book confuses FK with her husband F. Ellis Kelsey by misstating authorship of an article on fetal studies on quinine (p. 168), but otherwise, the American information agrees with other sources.

“Sleeping Pill Nightmare.” *Time*, 23 February 1962, 86–7.

This article describes the European thalidomide tragedy. It mentions that the “cautious” FDA had restricted it to investigational use. This is only a half truth. At this time, the FDA had no control over testing; the FDA did not even have to be notified of it. The FDA could only restrict it from being sold. This article is important because it is the first mention of the thalidomide’s tragic side-effects in the U.S. popular media. This announcement of the tragedy gets little attention, partly because of the minimization of the affect on Americans. In fact, many sources list the NYT’s April article by Plumb (*above*) as the first.

Somers, G.F. “Pharmacological Properties of Thalidomide (α -Phthalidimido Glutarimide), a New Sedative Hypnotic Drug.” *British Journal of Pharmacology* 15 (1960): 111–6.

This describes thalidomide mouse experiments. It supposedly confirms that the drug promotes sleep, and has no deleterious side effects even in massive doses but hints that this could be due to non-absorption. These tests were to show thalidomide’s British distributors (Distillers) that it was non-toxic; it also refers to other studies that confirm human safety (see *Burley* above). Noticeably missing is fetal testing. This illustrates the incomplete testing of thalidomide.

_____. “Thalidomide and Congenital Abnormalities (Letter to the Editor).” *Lancet* 1 (28 April 1962): 912–3.

Dr. Somers, working with rabbits instead of mice (see above) is able to induce the deformities that are seen in humans with thalidomide; in fact, he states that his chief animal technician has never seen such deformities in his 50 years of rabbit breeding. Regretting his earlier omission, he suggests that this testing should be used to screen all new drugs for teratogenic properties. This supports this project’s point that synthetic drug testing standards were still developing.

Speirs, A.L. “Thalidomide and Congenital Abnormalities.” *Lancet* 1 (10 February 1962): 303–5.

This study isolates the cause of the deformities to thalidomide by questioning the mothers of deformed babies about radiation, nutrition, infection, and drug usage. This is used to illustrate corporate greed because Grünenthal continues to blame other factors after this study is published.

Taussig, Helen B. “The Thalidomide Syndrome.” *Scientific American* 207 (August 1962): 29–35.

Dr. Taussig, a noted U.S. pediatrician, went to Europe to investigate phocomelia’s rise. She mentions FK’s role in thwarting its U.S. sales. Published nearly simultaneously as FK’s story, this article stresses the drug’s side-effects, and also warns that it was distributed for U.S. clinical tests. This article provides many details about Dr. Lenz’s study, excessive drugmaker’s marketing, and details of thalidomide’s fetal effects, and these are used in this project.

“Television.” *NYT*, 2 August 1962, 53.

The daily television schedule shows that FK “who blocked the sale of thalidomide in this country” will appear on the TODAY show. This show was (and still is) known for broadcasting the views of influential people. This is important because it shows that FK had the means to influence FDA changes.

“Thalidomide and Congenital Malformations (Editorial).” *Lancet* 1 (10 February 1962): 307–8.

Lancet, a respected medical journal, editorially agrees that thalidomide caused birth defects, and chastises the drugmakers for neglecting fetal tests. This illustrates this paper’s point that drug testing standards were still being debated in this era.

“Thalidomide Opponent Named to Head New U.S. Drugs Unit.” *NYT*, 29 December 1962, 1.

This front page article announces the reorganization of the FDA shortly after its regulations were strengthened. The new branches address its expanded mission of evaluating safety and efficiency, and surveillance of drugs. FK is to head the unit which determines which drugs are to be tested on humans. This is used to show that the FDA's new focus is safety through scientific methods.

“Thalidomide Pill was Tested in U.S.” *NYT*, 28 July 1962, 15.

This article discusses the extent of thalidomide's U.S. clinical testing (actually underestimated here), and discusses the need to strengthen laws to give the FDA more control over research use. This supports this paper's contention that unregulated clinical testing was an FDA weakness.

Thalidomide Victims Assoc. of Canada web-site. <<http://www.thalidomide.ca>>. Accessed: various dates.

TVAC seems to be the most interactive English-speaking Thalidomider group. This web-site provided much first-hand information about living with the drug's deformity, as well as their involvement in the FDA approval of thalidomide.

“This Month's Feature: The Investigation of the Drug Industry.” *Congressional Digest*, February 1962, 35–64.

This is an extensive collection of articles that analyze the Senate Subcommittee on Antitrust and Monopoly investigation led by Sen. Estes Kefauver, D-Tenn. starting in 1959. Short of reading the 26 volumes generated by this nearly 3 year investigation, this offers excellent insight on key issues, and contains Senate testimony from the chairman of the Pharmaceutical Mfrs. Assoc. and a debate between the key players: Pro (Kefauver) and Con (Senators Wiley R-Wisc., Dirksen R-Ill., Hruska R-Neb.). It is important to this project because it shows the drugmakers' strong opposition to regulation, the emphasis on pricing over safety concerns, and the stalemate prior to the thalidomide tragedy.

“Tighter rein on drug testing.” *Business Week*, 12 January 1963, 76+.

This provides a summary of the testing rules that the FDA implemented based on the new Kefauver-Harris Amendments, and how the drug industry feels about them.

“Tough drug law coming.” *Business Week*, 11 August 1962, 37.

This article gives the business point of view on the thalidomide-inspired safety reforms being discussed in the Senate. It tries to convince the reader (with questionable statistical analysis) that the link between thalidomide and phocomelia has not been definitely proven. It points out that the drug industry seems ready to concede, even though the head of the Amer. Pharm. Assn. thinks they are giving too much away because of the public's emotion. It attributes that emotion to the disclosure of FK's actions. This supports a point of this paper: FK inspired reform.

“Tragedy From a Pill Bottle Some Sad Lessons Learned.” *Newsweek*, 13 August 1962, 52–4.

This article contains: a summary of the European thalidomide tragedy, an analysis of the FDA's weaknesses, and speculation what might have happened if not for FK's actions. It contains FDA statistics (such as number of drug investigators) which are also included in this paper.

“Trial Drug Curb Sought By FDA.” *St. Paul Pioneer Press*, 29 July 1962, 1st section, 1.

This appears shortly after FK's actions have been publicized. It is useful to this project because it clarifies the not “widely known” facts that drug firms controlled clinical tests and were not required to inform its subjects. This shocked Americans into supporting stronger drug regulations.

“The Unfinished Story of Thalidomide.” *Saturday Review*, 1 September 1962, 35–40.

This article discusses the FDA, both pre- and post-thalidomide tragedy. The details of the FDA’s drugmaker favoritism show that the pre-tragedy FDA was inadequate at drug regulation. The details on the post-tragedy controversy caused by Larrick’s delayed thalidomide show that FK caused the FDA to change direction, from drugmaker advocate to consumer advocate.

United States. Congress. Senate. Committee on Government Operations. Subcommittee on Reorganization and International Organizations. Interagency Coordination in Drug Research and Regulation. Part 1[microform]: hearings before the U.S. Senate Committee on Government Operations, Subcommittee on Reorganization and International Organizations. 87th Cong. 2nd sess. pt. 1 (1 August 1962).

After FK reveals her actions, and Larrick finally issues a recall of the thalidomide used in clinical testing, they are called by Sen. Humphrey to testify. This contains useful details on these events, and it is also notable for the difference in treatment of the two witnesses. Larrick is intensely questioned about Merrell’s rampant clinical tests and the recall’s delay; he becomes very defensive. FK is praised and asked for her input on how to improve drug regulation.

_____. Congress. Senate. Thalidomide and other Drugs. 87th Cong. 2nd sess. *Congressional Record* 108, pt. 12 (8 August 1962): 15932–5.

This is a chronological record of FK’s FDA investigation of thalidomide. It documents nearly 60 interactions with Merrell representatives; they become increasingly upset with her refusal to accept the application. It clearly shows the intimidation tactics used by Merrell and FK’s refusal to accept substandard tests. This shows her tenacity and dedication to her mission, making her not only a heroine, but also a role model for reform. It is also important because Kefauver, by publicizing it before the Senate, showed his political savvy; this helped him gain the support for his strong reform bill, which eventually passed unanimously.

_____. Congress. Senate. Drug Legislation. 87th Cong. 2nd sess. *Congressional Record* 108, pt. 12 (9 August 1962): 16072–4.

This is a record of a discussion on the drug legislation after FK gave her suggestions for FDA reform in a Senate subcommittee hearing (led by Sen. H. Humphrey). Here, Sen. Kefauver relates FK’s suggestions and actions (blocking thalidomide) to his proposed bill. This supports this paper’s thesis that she inspired and was a model for reform.

_____. Congress. Senate. President’s Letter to Sen. Eastland on Amendments to Drug Laws. 87th Cong. 2nd sess. *Congressional Record* 108, pt. 12 (23 August 1962): 17371–2.

This is a record of a letter dated April 10, 1962 that President Kennedy sent to Sen. Eastland requesting a few basic drug regulations replace Kefauver’s more restrictive bill so that something could be accomplished in the wake of the thalidomide tragedy. This information is used in this paper. Also interesting, it appears in this August record (after FK revealed her story and influenced support for Kefauver’s more restrictive bill) to show that the President had withdrawn support for his weaker April 10 request and now favors the reinstated Kefauver measures.

_____. Congress. Senate. Senator Douglas after vote on Amendments to the Federal Food, Drug, and Cosmetic Act. S. Res. 1552. 87th Cong. 2nd sess. *Congressional Record* 108, pt. 12 (23 August 1962): 17422.

This is the record of the official Senate vote for Kefauver's (and FK inspired) drug safety regulation bill (S.1552). It passed 73-0. It is important because of how quickly it passed after FK's story was published (5 weeks) even though it was more restrictive on the drug industry than any of the proposals made in the prior 3 years. It is also important because Sen. Paul Douglas made a speech praising Kefauver for enduring the long battle; his closing line to that speech is one of the introductory quotations of this paper.

_____. Congress. Senate. Approval of Senate Bills and Joint Resolutions After Sine Die Adjournment. S. Res. 1552. 87th Cong. 2nd sess. *Congressional Record* 108, pt. 14 (13 October 1962): 23473.

This records that President Kennedy signed the Kefauver-Harris Amendments (S.1552) on October 10, 1962. The time between FK's story and the signing (after unanimous approval in both houses of Congress) is 3 months — previously Kefauver had battled for over two years with no consensus. This supports this paper's thesis that FK was a motivation for reform.

“U.S. Considering Regulations to Reduce Peril of New Drugs.” *NYT*, 29 July 1962, 44.

This article details Merrell's thalidomide's recall from clinical trial. Merrell says the recall began in March, which is stretching the truth — they wrote a letter to doctors saying there is still much doubt about a causal relationship between the drug and the deformities, but doctors should not give the drug to potential mothers. This is important because this public announcement is only a few days after FK reveals her story, which is why she told it.

Warren, Randolph. “The Last Word — Living in a World With Thalidomide: A Dose of Reality.” *FDA Consumer*, March–April 2001. From FDA website, available from http://www.fda.gov/fdac/departs/2001/201_word.html. Accessed 19 February 2007.

The author is a thalidomider and former president of the Thalidomide Victims Association of Canada. This is useful for his perspective on the pending FDA approval of the drug; interestingly, the FDA invited them to be involved in these deliberations.

_____. “The Many Faces of Thalidomide.” 7 May 1999. From Thalidomide Victims Association of Canada website, available from <http://www.thalidomide.ca/en/information/faces.html>. Accessed 19 February 2007.

This is a current listing of the countries where Thalidomide had been sold or distributed, the dates of availability, and the trade names used. These appear in this project.

White, Anthony. “German Doctor Linked Drug to Deformities.” *St. Paul Pioneer Press*, 12 August 1962, 1st section, 10.

This article is important for several reasons. It includes an interview with Lenz about his discovery of thalidomide's link to phocomelia. It also notes that Grunenthal believes that Lenz's case against thalidomide is still unproven. Finally, it highlights this era's flawed and dangerous testing philosophies. Drugs typically were not clinically tested on pregnant women because they were “in a biologically exceptional category and not suited for such tests;” however, doctors prescribed these drugs to pregnant women because they had not been shown to be harmful.

Secondary Sources:

Bren, Linda. Journalist for *FDA Consumer* magazine. E-mail interview by the author. 23 February 2007. Ms. Bren interviewed Dr. Kelsey for the article below. She said that Dr. Kelsey is now retired and is no longer granting interviews due to illness. Ms. Bren suggested other resources, however, and they are used in this project.

_____. "Frances Oldham Kelsey: FDA Medical Reviewer Leaves her Mark on History." *FDA Consumer*, March–April 2001. From FDA website, available from http://www.fda.gov/fdac/features/2001/201_kelsey.html. Accessed 1 February 2007. This is a biographical article on FK written while she was still working for the FDA (she retired in 2005 after 45 years). In parts, this article can be considered a primary source because it contains many quotes gathered by Ms. Bren during an interview with FK. Details and quotes about FK's background and her contributions appear in this project.

Fontenay, Charles L. *Estes Kefauver: A Biography*. Knoxville: Univ. of Tennessee Press, 1980. Chapter 19 of this biography of Tennessee Senator Estes Kefauver details his congressional efforts to improve drug regulation. This is useful for details on his political maneuvering and the roles that thalidomide and FK played in the shaping of the Kefauver-Harris Amendments.

Gorman, John Bruce. *Kefauver: A Political Biography*. NY: Oxford Univ. Press, 1971. This is the political history of Tennessee Senator Estes Kefauver, a populist Democrat. It provides details on his campaign for more control of the pharmaceutical industry, both in pricing and safety, which is useful to this project.

Hawthorne, Fran. *Inside the FDA: The Business and Politics Behind the Drugs We Take and the Food We Eat*. Hoboken: John Wiley & Sons, Inc., 2005. This current analysis of the FDA provides important background, especially Chapter 3: The First 100 Years, Chapter 6: Case Study: The Return of Thalidomide, and Chapter 7: How Picky is the FDA? Especially, two points are useful here: FK is attributed with modeling effective drug safety, and business cannot be trusted to market safe drugs; government regulation is critical.

Hilts, Philip J. *Protecting America's Health: The FDA, Business, and One Hundred Years of Regulation*. NY: Alfred A. Knopf, 2003. This is an excellent source of information on the history of the FDA and also has an extensive bibliography. It is used as general background as well for specific areas such as the formative years of the agency, budget cuts and reduced staffing, a quote from Winton Rankin, deputy Commissioner on Larrick's closeness to the drug industry, and a quote from the author on the FDA's worldwide impact.

Insight Team of *The Sunday Times* of London. *Suffer the Children: The Story of Thalidomide*. NY: Viking Press, 1979. This book was written by a group of journalists who covered the thalidomide court cases in England. It provided excellent details on the events surrounding the thalidomide tragedy. It is used for information about Grünenthal, their experiments in developing thalidomide, and thalidomide's marketing. Especially interesting was the description of the bizarre testing techniques ("jiggle cage") used to determine if thalidomide made mice less active.

Patrick, William. *The Food and Drug Administration (Know Your Government)*. NY: Chelsea House Publishers, 1988. This is an excellent concise description of the FDA's mission, history, and organization and is used in this project for the history of the early development of the FDA.

Stephens, Trent and Rock Brynner. *Dark Remedy: The Impact of Thalidomide and Its Revival as a Vital Medicine*. Cambridge, MA: Perseus Publishing, 2001.

Written by an embryologist who has been researching thalidomide for 25 years and a historian, this book is used for information about the drug industry in post-WWII Germany. It is also useful for information about the current uses of thalidomide and its recent approval. This recent book tells about the current conditions of the thalidomide babies as adults.

United States Food and Drug Administration web-site. <<http://www.fda.gov>>. Accessed: various dates. This web-site provided background information on the history of the FDA, as well as details on its mission, organization, procedures, future plans, and details and statistics on drug regulation. Especially useful was the information on thalidomide, both the history and its uses today.

Illustration Sources:

Page 2 (top): <http://www.contergan-hamburg.de/contergan_2.html> Accessed: 25 February 2007.

Page 2 (btm): Brochure about Neurosedyn (trade name of thalidomide). c. 1961. Astra Pharmaceuticals, Sweden. <<http://www.art-bin.com/bilder/neurosedyn.jpg>> Accessed: 28 February 2007. Brochures text (in English): Barbituric acid-free hypnotic and sedative for children.

Page 3: Spiers, A.L. "Thalidomide and Congenital Abnormalities." *Lancet* 10 February 1962: 304.

Page 6: <<http://www.genarians.com/images/F.O.%20Kelsey.jpg>> Accessed: 4 Mar. 2007.

Page 8: Sjöström, Henning and Robert Nilsson. *Thalidomide and the Power of the Drug Companies*. Middlesex, England: Penguin Books, 1972. Page 156.

Appendix: *LIFE*, 10 August 1962, 29.

Source for paper format:

Turabian, Kate L. *A Manual for Writers of Term Papers, Theses, and Dissertations*, 6th ed. Revised by John Grossman and Alice Bennett. Chicago: University of Chicago Press, 1996.