broke protocol with the Merrell application, however, assigning it out of turn to a newcomer. They wanted forty-six-year-old Frances Oldham Kelsey, Sjoerdsma's University of Chicago pharmacology acquaintance, to have an easy first case. Kevadon looked like a rubberstamp.[2]

Kelsey surprised everyone.

Thalidomide was then the third best-selling drug in West Germany. Sold as a single agent, or in combination with other drugs, in about forty-five other countries, it was a simple chemical preparation that appeared singularly safe.

The West German firm, Chemie Grunenthal, first synthesized the drug in 1953 and marketed it, in 1956, as Grippex®, to treat colds and influenza. A year later, looking to maximize its profits, the company reintroduced thalidomide as Contergan®, a mild, non-toxic sedative and hypnotic that was available over the counter. Unlike other sedatives, thalidomide posed no danger of an accidental or intentional overdose—a major selling point. Grunenthal licensed the drug's manufacture to other companies around the world, including Merrell.[3]

Despite thalidomide's widespread use and popularity—indeed, because of its anticipated mass circulation among healthy Americans—FDA neophyte Frankie Kelsey scrutinized Merrell's NDA. Assisted in her review by pharmacologist Oyam Jiro and chemist Lee Geismar, she found deficiencies in the company's animal and clinical data.

The clinical reports "were really more testimonials than scientific studies," Kelsey recalled, and the company's claims seemed "too good to be true." Before she could sign off on Kevadon, she needed to be certain about the drug's safety.[4]

> *Thalidomide came across as the perfect hypnotic, but, if so, it would be used in a huge population, so you could understand Kelsey's concern. I had no vested interest in the drug, but I knew it was a damn good drug, and people were going to Europe to get it.*

Under the 1938 drug act, whose terms Professor Geiling helped to define, the FDA had sixty days after receipt of an NDA to raise objections. Absent an exception, product approval was automatic. But a medical reviewer could extend the evaluation period, effectively tolling time, by asking the manufacturer for more details. Kelsey repeatedly invoked this loophole, postponing her decision on Merrell's NDA for months.

On Nov. 10, 1960, Kelsey and her colleagues sent their first letter to Merrell, outlining problems they had observed and requesting better evidence on toxicity.[5] On Jan. 17, 1961, after what Kelsey characterized as "a number of conferences and phone calls" between her and Merrell—chiefly with Dr. Joseph Murray, who aggressively lobbied her to approve Kevadon—the company resubmitted its application. In the intervening weeks, however, further reason to question the U.S. import of thalidomide arose.

According to a physician's report in the Dec. 31, 1960, issue of *The British Medical Journal*, some patients treated with thalidomide had developed peripheral neuritis, with a painful tingling of the arms and feet.[6] Because of a mail strike, Kelsey's copy of the *BMJ* did not arrive until weeks after publication, and it was Feb. 23, 1961, when she finally notified Merrell of the adverse reaction report (ADR) and asked for a list of investigators involved with thalidomide. Murray and another company official flew to England and West Germany to investigate the ADR and eventually downplayed the neuritis as rare and reversible upon discontinuance of the drug.[7]

But Kelsey was not so sure. She now not only questioned the drug's safety, but Merrell's candor, suggesting that the company had known of the peripheral neuritis cases before filing its NDA. That Canada approved the sale of Kevadon in April 1961 did not assuage her concern.

Fortuitously, during Kelsey's exchange with Merrell, European obstetricians began to document a disturbing, unexplained trend of terribly deformed babies being born. Some of these babies lacked arms and legs, while others had severely stunted limbs, no external ears, and malformed digestive systems.

Alarmed by an outbreak among newborns in Hamburg, West Germany, of phocomelia, the term for flipper-like limbs, Dr. Widukind Lenz, an expert in teratogenesis (birth-defect causation), researched the history of the condition's incidence and conducted open-ended interviews with mothers of the children. By mid-November 1961, he knew of fourteen cases of birth defects in which the mothers had taken thalidomide during pregnancy to induce sleep. Thalidomide also, incidentally, alleviated morning sickness, but it was not marketed for this purpose, as is commonly misunderstood. Lenz submitted his data to Chemie Grunenthal. On Nov. 28, 1961, under pressure from German health officials, the company withdrew all forms of the drug.[8]

For several months, Merrell scrambled to save thalidomide in the United States, suggesting an alternative anti-cancer use, but the FDA balked. The company finally rescinded its NDA in March 1962. Although Kelsey had asked Murray about the safety of thalidomide use during pregnancy, she had been concerned about peripheral neuritis, not congenital abnormalities. During her World War II malaria research, Kelsey had observed that quinine more profoundly affected a rabbit fetus than its mother. She thought the same might be true with thalidomide, but she never envisioned the serious birth defects that forced Grunenthal to withdraw the drug.[9]

After Merrell pulled its NDA, the FDA took no further action. Then, on April 6, 1962, Dr. Helen B. Taussig, a Johns Hopkins pediatrics professor and congenital heart defect expert, contacted Dr. John O. Nestor in the agency's Division of New Drugs. A pediatric cardiologist associated with Children's Hospital in Washington, Nestor also was known for his attempts to compel lawfulness on area highways: To drive at the posted speed limit in the far left lane of the D.C. beltway was to "nestorize" the loop.

Taussig had co-developed the successful surgery for "blue-baby" syndrome, a congenital cardiac or pulmonary defect that depletes an infant's blood of oxygen and, thus, causes cyanosis. The highly respected professor had seen German babies with phocomelia and agreed with Lenz that thalidomide—not a hereditary factor—was responsible for this extremely rare and tragic bone malformation. Taussig briefed Nestor and Kelsey on the epidemic and began to disseminate her findings to the U.S. medical community, pointedly telling an audience of doctors in Philadelphia that "this compound could have passed our drug laws." The only reason it hadn't, she said, was because Merrell had submitted "insufficient data" in its NDA.

The next day, a secretary in U.S. Senator Estes Kefauver's office read a *New York Times* article about Taussig's speech and showed it to Kefauver's chief economist, John M. Blair. Blair immediately commissioned a full report on thalidomide.[10]

Since 1958, Blair and the staff of Kefauver's Subcommittee on Antitrust and Monopoly had been investigating price-gouging by the pharmaceutical industry. The Populist senator from Tennessee was now convinced that drug companies were marking up their prescription

drugs exorbitantly, vis-à-vis the cost of generics. Kefauver also believed physicians' claims that antibiotic advertisements in medical journals were either misleading or fraudulent.

> *Kefauver was investigating the price of antibiotics. He thought there was collusion among the drug companies. I have no idea if there was or not, but there may have been.*

Tall and lanky, Kefauver had run unsuccessfully with former Illinois Governor Adlai E. Stevenson in the 1956 presidential race. Known for the coonskin cap he wore while campaigning, Kefauver spoke in an agonizingly slow manner, a Southern affect that concealed his shrewd and intelligent mind. A 1927 graduate of Yale law school, Kefauver had long been interested in protecting small businesses from corporate monopolies.

The senator started holding hearings on drug prices in December 1959, initially focusing on steroids, then tranquilizers, oral antidiabetics, and antibiotics. In the process, he exposed enormous differences between companies' manufacturing costs and the prices they charged the public. Opposing him in the debate was political titan and subcommittee member, Senate Minority Leader Everett Dirksen (R-Illinois), who insisted that the cost to industry of drug research, production, distribution, and sales justified price markups.[11]

Just as today, the patent law gave an inventor an exclusive right to make, use, and sell an invention for seventeen years. During this exclusivity, pharmaceutical companies, which could license the use of a new drug, presumably recouped the capital they had invested. Kefauver sought to change patent protections by reducing companies' time of exclusive control (he leaned toward five years) and obligating them to agree to less lucrative licensing contracts. Dirksen vociferously argued that the industry needed such protections as an incentive to invest in research.

The Kefauver hearings played out for months, drawing hundreds of spectators, prompting coast-to-coast headlines, and attracting the attention of industry, physicians in private practice, and anyone connected to or interested in either, including Sjoerdsma and his colleagues at the National Heart Institute. Finally, on April 12, 1961, the senator introduced legislation to amend the 1938 drug law. His Senate Bill 1552:

- required drug patent holders to license their products, with a royalty payment of up to 8 percent of sales (twice as much as the standard), after three years of exclusivity;
- authorized the FDA to license all drug manufacturers, who would be subject to strict quality-control standards and government inspection of their plants;
- mandated explicit warnings about a drug's side effects and a statement about its "efficacy" (effectiveness) in advertisements;
- required the FDA to certify the strength, quality, and purity of antibiotics;
- gave the FDA open-ended authority in ruling on NDAs, thus ending the sixty-day deadline; and
- required manufacturers to prove drug efficacy, as well as safety.

A year later, when Kefauver's economist, Blair, learned about the thalidomide catastrophe, what remained of S.B. 1552 lay gutted in the Senate Judiciary Committee. To make matters worse for the senator, President Kennedy had sent his own drug company-friendly bill to Capitol Hill in April 1962. Representative Oren Harris (D-Arkansas), chairman of the House Interstate and Foreign Commerce Committee, introduced the White House's H.R. 11581, which contained no patent provisions and no measures to help lower drug prices.

Kennedy had vied bitterly with Kefauver for the 1956 vice-presidential nomination, but his motivation in breaking with the Tennessee senator was practical, not personal. In his State of the Union message, the President had proposed a federal program of medical care for the aged, and he wanted industry to support it.

On July 12, 1962, after much political maneuvering, the Judiciary Committee approved a substantially revised S.B. 1552 that contained only fifty-five lines of Kefauver's original draft. Confronting almost certain defeat, Blair decided to leak the thalidomide story. *The Washington Post* broke it on Sunday, July 15, 1962, the same day that Frankie and Fred Kelsey attended a back-yard barbecue at the Sjoerdsmas' home. After enjoying her customary Manhattan, Frankie took a phone call from an NBC radio reporter and gave a nationally broadcast interview from Fern Sjoerdsma's office. The quiet, studious woman became an overnight celebrity.[12]